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MECHANISMS OF AGING*

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In order to evaluate certain current researches on the basic problem of aging, it immediately becomes necessary to establish certain definitions. These can be only tentative until more exact information is available.

The manifestations of aging are apparent to all. The finer alterations, those subtle changes that appear particularly in the spheres of the emotions, intellect and conduct, may escape the unpracticed eye. These are important. They require the scrutiny of the experienced clinician to assess the degree of degradation. As more exact methods become available for estimating changes either of body or behavior, the practicing geriatrician will enjoy a more detailed diagnostic armamentarium for service to his clientele.

AGING AND THE AGED

Nearing the end of a long life, when primary faculties are impaired or lost and the individual is no longer capable of self determination and support, he is recognized as "aged." When biologic deterioration has advanced beyond the point where restoration is possible, society must arrange for custody and T.L.C. (tender loving care).

Services relating to these aged people are in an entirely different category than those centering on the changes of body and mind that appear with advancing years. The nature of these alterations is our first field of inquiry.

Individual growth and development is characterized by certain progressions emanating from and originating in each cell of the body. There appears to be an optimum span of function for each cell, organ and system. This varies with function. The placenta dies at birth. The thymus shrinks shortly before puberty. The ovaries cease function at the time of the menopause.

It is possible to cultivate tissues and have them live in an unorganized state for months beyond their usual existence. Such studies have only a limited value, since the tissues are sustained in a nutrient that is alien to body fluids and also lack the interrelationships that exist in the living organism.

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THE MAJOR INVOLUTION

Decline and senescence are later stages of normal growth and development. Warthin (1) has called old age the major involution. Since his era some forty years ago, it has been shown experimentally that with restricted diet, more exercise and administration of hormones, the life span of certain animals can be greatly extended. The data on man also point to a longer life. These advances are the result of better hygiene and sanitation, more effective control of certain infections and a clearer knowledge of nutritional needs. This is the most promising field for exploration concerning the continued growth and development of an individual throughout his entire life. There would be recognition of the fact that changes (recession) in cells and organ systems which are classed as due to aging are, in reality, one phase of continuation (of growth and development). This point is important. It focuses attention on the necessity for resisting in every way the tendency to inactivity and withdrawal as a person ages.

The description of tissue sections from old bodies is not especially helpful in gaining information on the dynamics of tissue deterioration.

DYNAMICS OF GROWTH

In the living state, cells and organ systems are in a continuous state of change, of transformation; nutrition flows in and waste products flow out, across cell membranes. The vitality of the cell, at least in theory, can be enhanced by more specific nutrition plus activity. That is, a healthy cell is one characterized by optimum diet and activity. Detrimental influences are introduced by alteration in diet, loss of function (activity), and external agents such as infection or trauma. If it were possible to measure the survival potential of each cell's system it would be possible to estimate the life span of that tissue.

The measure of aging becomes an estimate of the kinetic decline of vitality. With cells in a perpetual flux of renewal and concurrent degradation, the point of first decline is established the instant deterioration tops renewal. It should always be kept in mind that the human body has an amazing exchange mechanism, an inbuilt ability to renew itself. Such plasticity offers the possibility of extended performance, once the basic requirements of the cell and organ systems are known. This is where we are today. The situation calls for a return to a study of the cell, not as it is affected by disease and deterioration solely, but with emphasis on its potential growth and development. From this viewpoint, emphasis is placed where it belongs. Senescent changes may, in theory, be delayed by better understanding of cell hygiene.

Concentration on this approach at present is highly encouraging. The use of the new techniques with radioactive tracers to chart the refined progression (catabolism and synthesis) of food elements, hormones and chemicals as they are introduced into the body has already revolutionized our knowledge of nutrition, and the functions of blood and other organs. Medical knowledge is in a state of rapid transformation. Weiss (2) has stated that neurons can divide and reproduce themselves. In response to demand (stimulation) the nucleus and cell body of a nerve cell enlarge; conversely, neurons deprived of excitation atrophy and decay (age).

The aging of connective tissue, composed mostly of collagen, is of particular interest because it constitutes the supportive architecture of practically the entire body. Connective tissue is the sustentacular framework for the specialized cells in every organ. In old age, disturbances of the connective tissue framework and of its principal component, collagen, appear clinically in the form of various kinds of arthritis, rheumatism and skin diseases, all of which are grouped under the term collagen disorders. Even arteriosclerosis is designated by Verzár (3) as a disturbance of connective tissue.

Collagen is chemically composed of chains of polypeptides containing many glycine and hydroxyproline residues. These filamentary molecules are arranged in groups of 3, to form helices. Each set of 3 helices makes up a "super-helix," and so the process continues, the "cable" ever increasing, until it becomes visible under the microscope. Thermal contraction, according to Verzár, is in reality an acceleration of aging. Some interesting studies of collagen labelled with carbon (C^{14}) or tritium have been carried out by Verzár, Tunbridge and others. In aging of the skin, for example, the tissue of collagen fibers becomes altered to resemble that of elastic fibers, as shown by staining their enzymatic reactions and also by examination with the electron microscope. Under this microscope young collagen fibers exhibit an orderly periodic structure, whereas elastic fibers are structureless. As the collagen fibers change with age, the skin loses elasticity and wrinkles appear—one of the characteristic findings of the elderly skin. When collagen fibers are heated to 62°C. they shrink to approximately 30 per cent of their former length, as demonstrated by Verzár. As the result of thermal contraction, collagen fibers become resilient and resemble elastic fibers in various aspects. In this process of heating, the beautiful helical outline of collagen disappears and the fibers become transparent, resembling elastic tissue.

Upon heating collagen, hydroxyproline and a mucopolysaccharide are liberated, and, at the same time, the helix structure disappears. Any influence that produces loss of the helix structure changes the tissue of collagen fibers to that resembling elastic fibers, *i.e.*, a transparent residue which is probably a mucoprotein. The elastic component of polypeptide chains alters with age. This can readily be demonstrated. For example, as shown by Clive McCay (4) and his students, collagen fibers from tails of old rats will contract more forcibly when heated than those from young animals. This may be due to cross-linkages formed between polypeptide chains. These linkages may be hydrogen bonds which form in greater numbers with increasing age. Thus, the filamentary molecules become interconnected and appear to increase in structure or, as Verzár states, they become more rigid than collagen fibers from young animals. This process of increasing cross-linkage between filamentary molecules theoretically might be applicable to the aging of other body proteins. Further cross-linkage presumably may take place in the chromatin of the chromosomes in old animals, thereby leading to abnormal cell division. Changes as described might help to explain how the aging body and its various systems tend to become more rigid and less adaptable with the passage of time.

Cowdry (5) has observed the life cycle of certain types of cells. He believes the cells of the dermis and certain cells of the eye to be practically immortal. Carlson

and others have expressed their belief that the human organism has never yet been allowed to live its allotted span.

DEFICIT LIVING

If it were possible to concentrate on certain tissues, such as bone, muscle, endothelium of arteries and nerve cells, and protect their growth and functional integrity, the body would enjoy an amazing increase in performance and durability.

For example, osteoporosis is almost universal in the elderly. Yet, by diet and generous exercise it can often be avoided. Endocrine factors are involved, but with exercise and adequate food the skeleton can frequently be strengthened.

Muscular performance (physical fitness) can be greatly improved by regular exercise. In our experiments on comparing the ability of subjects of various ages subjected to a standard stress (measured by a bicycle ergometer), older persons in training held their own and often exceeded the capacity of younger persons who were not accustomed to regular exercise.

Better circulation to the brain will protect the vitality of nerve cells.

THE NEED FOR COORDINATION

With sharpened interest in the cellular vitality of bones, muscles and nerves, the body as a whole may be better understood. As the result of knowledge now in the making, a more durable frame and organ system will permit the individual to anticipate an extended existence.

The extreme isolationism of research areas which now exists needs to be corrected. The nutritional chemist, the experimental biologist, the endocrinologist and the sociologist have ideas of first importance to the clinician. Yet, they have not met in a common purpose. Each has much to learn from the other. It is apparent that the clinician must return to the fields of structure and function to learn more of what is going on in the growth, development, maturation and decline of the body. Otherwise, the clinician will continue to deal with end-results; his stock in trade will be repair work only.

We like to regard medicine as a progressive art and service. To demonstrate this ideal, medicine needs to broaden its horizon. While starting at the autopsy table and working backward, it is of at least equal importance to dwell on the positive phases of normal growth and development. Prevention of disease should lead to a positive approach. Geriatricians should acquire interest in activities which strengthen the body and refresh the mind. No one individual in the family of science is so well equipped as the clinician to act as the coordinator in bringing all the disciplines together on the basic issues.

CONCERNING MATURATION

Medicine is continually perplexed and usually not satisfied in its appraisal of conditions arising in the twilight zone of body-mind relationships. The failure to achieve success in therapy in so many instances thwarts us. The patient, in trying to attain "peace of mind," baffles the practitioner.

This field assumes added interest when the new dimension of added years for man resumes a reality. The how of longer life changes to why. Are men and women to be condemned to an extended life of indolence, immaturity and sufferance? If the average span of human life is to be a round century—and this may well become a reality in the latter half of the twentieth century—the content of added years, in terms of enduring satisfactions is the first goal that faces science. The neurophysiologist has no key to these issues. So far as the various phases of the life span, growth, development, maturation and senescence are concerned, the goal to be desired is optimum health and interesting activity as long as persons can carry on with substantial reserve and delay of senescent changes.

It is probable that no definition of maturity will ever satisfy every critic. Any statement will be assailed, depending upon one's field of interest. A healthy body with a healthy mind in every person who is socially responsive and self-sustaining, among other qualities, would seem essential.

GERIATRIC RESEARCH PRIORITIES

The spontaneous success of the American Geriatrics Society since its creation seventeen years ago, and the rapid increase in membership indicate an interest in the problems of older age. The membership represents a cross-section of all fields in medicine. This is a healthy sign. At this time it is appropriate to raise certain questions. What is the aim of our organization? What does the membership expect to derive from its meetings and publications? Since aging extends across and through the entire spectrum of human growth and experience, it is evident that certain limited areas need be selected for inspection and research. Prior to any social or political components, the biologic aspect should be more intensively explored. Medical service has a preferential opportunity, indeed an obligation, to demonstrate some creative imagination and intellectual resourcefulness in crystallizing the most promising direction of inquiry. This requires a new start, a return to fundamentals.

There is already a vast amount of data bearing on individual health and happiness in later years. There is fruitful research in progress. Classification and streamlining of such information is one of our obligations. The correlation and integration of this knowledge can only be carried out by our experienced clinicians. Here we find our best opening.

Should this society sponsor and support research? There can be only one answer. The convening at regular intervals of research symposia such as the one on nutrition last year in California, is most timely.

Victor Hugo observed: "There is nothing in the world so powerful as an idea when the time has come."

Fortunately, I believe, the American Geriatrics Society has reached flood tide. Since its founding it has enjoyed phenomenal success. No other medical group has a single focus on the health of the elderly as does this organization. Science has recently elaborated techniques of exquisite precision with which to probe the fascinating unexplored field of human aging. Comparatively little research has been organized. The nature of tomorrow's world will be in large measure de-

pendent upon the answers to many questions relating to the continued growth and development of human beings as they enjoy added years. Too much emphasis has been placed upon the negative aspect of aging. The more exciting approach should highlight the enduring satisfactions that may be experienced as men and women attain the summit of their years and then continue on that plateau nearer and nearer to the century milestone.

Whereas the basic scientists make up the advance wave of all who are students in this fascinating field, the clinicians are the shock troops who must daily be available to guide the older patients and their families in the course to be followed. Life is short, the art long, the occasion instant, experiment perilous, decision difficult. We clinicians are under pressure of rapidly increasing intensity to lead our older citizens to a more satisfying longer life.

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EFFECT OF SATURATED AND UNSATURATED FATTY ACIDS UPON HEPARIN-RETARDED CLOTTING TIME*

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During the course of a study of the effect of the steroids upon heparin-retarded clotting time (HRCT), we observed some fairly wide fluctuations, not only in the treated patients but also in the control subjects whom we had selected to establish a normal base-line. Several observations were made on each patient over a period of several weeks in both the steroid treated and non-steroid treated groups. In some instances, the initial observations were made with the subject fasting. All the steroid treated patients had rheumatoid arthritis and returned at regular intervals for observation, at which time the HRCT determination was repeated. The non-steroid treated patients had a variety of conditions which required periodic visits to the office; at each visit the HRCT was checked. After a few weeks' study it became apparent that there was a wide variation in HRCT in both groups. A review of our records revealed that almost invariably the value was higher in fasting than in non-fasting subjects. This suggested that food might influence the HRCT. A further analysis of our results indicated that the values varied according to the time of day, but that this variation was always in relation to food intake. We also observed that following a heavy carbohydrate intake, such as in a glucose tolerance test, the HRCT was increased. We then extended our study to include the effects of various foods.

The study of defects in the coagulability of the blood has a long and extensive history, but hypercoagulability has received only comparatively recent attention. Investigation has been given an added impetus since lipid metabolism has taken on a renewed significance in the search for the etiologic factors in atherosclerosis. It was noted by European surgeons during World War II that postoperative thromboembolic accidents were reduced during the years when the population was forced to consume a diet which was very low in fat (1). In 1949, Duncan and Waldron showed that there was a significant shortening of the silicone-tube clotting time after the ingestion of fat (2). This has been confirmed by Buzina and Keys (3) and others. Inhibition of fibrinolysis has also been demonstrated during the postprandial rise in blood lipids (4). There has been a great deal of speculation about the possible role of a state of hypercoagulability in the genesis of atheroma as well as of intravascular thrombosis. It has been proposed that hyperlipemic

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hypercoagulability may not only predispose to thrombosis but may also allow formation of mural clots, which may then become covered with endothelium and converted to atheroma by infiltration with cholesterol and other lipids (5).

We are fully aware of the state of chaos that exists concerning the role of lipid metabolism in atherosclerosis, and time will not allow us to discuss the pros and cons. Incidentally, there was no change in the HRCT with maintenance dosages of steroids, an observation which suggests that such dosages do not predispose a patient to thromboembolic phenomena. These data will be reported in detail in another paper.

MATERIALS AND METHODS

Two hundred and forty-seven patients were studied. For determination of the constancy of the HRCT, 200 patients were selected from the authors' office practice. There were 124 females and 76 males varying in age from 21 to 83 years; 62 patients were between 30 and 60 years of age. Various disease states were represented, but none that would influence the HRCT. The blood specimens were drawn between 8:00 and 9:00 a.m. with the patients fasting. Three or four observations at intervals of one to four weeks were made on each subject, for a total of 644 determinations. For the study of the effect of food and saturated and unsaturated fatty acids, 47 convalescing patients were selected from the wards of St. Clare's Hospital. There were 28 females and 19 males. The meals were given between 8:00 and 9:00 a.m., after a blood specimen had been drawn from the fasting subject. This group of patients had been admitted for a variety of conditions, but none had arthritis.

In order to magnify the changes observed in the standard venous clotting time, HRCT determinations were carried out according to the Waugh-Ruddick modification of the Lee-White technique (6). Four chemically clean test tubes (75 x 10 mm.), a syringe and a needle, were rinsed with isotonic sodium chloride solution. Into each test tube, 0.5 cc. of a sodium chloride solution containing 0.5 unit of heparin was placed by means of a 1-cc. tuberculin syringe. Following a cleanly negotiated venipuncture, 1 cc. of blood was placed in each tube, and the tube inverted twice to mix the heparin solution with the blood. Clotting was considered to have occurred when, following complete inversion of the tube, tapping of the tube with a finger did not produce movement of liquid blood.

RESULTS

The normal Lee-White clotting time is somewhere between 5 and 20 minutes, but in most instances it is between 5 and 10 minutes. The normal maximal variation of HRCT in our series was observed from 30 to 80 minutes after food intake, and 50 to 120 minutes fasting. There was considerable variation between subjects. However, when the fasting HRCT was established for a specific subject, it remained constant provided the blood was taken under the same circumstances at all times (Fig. 1).

Figure 2 shows the effect of age upon HRCT. There appeared to be a steady reduction of HRCT except in the sixth decade, when there was a slight increase; but a decrease occurred again in the seventh decade. We are unable to account for the rise in the 51–60 year age group, and we expect to repeat the tests in these patients to determine whether this is a false impression or whether there may be a real change.

Figure 3 shows the effect of a standard hospital breakfast containing about 450 calories of food with 18 grams of fat. There was a definite decrease in HRCT at

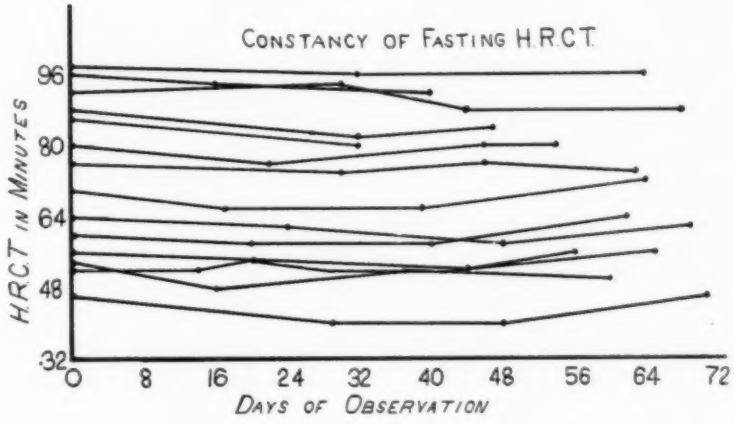

FIGURE 1

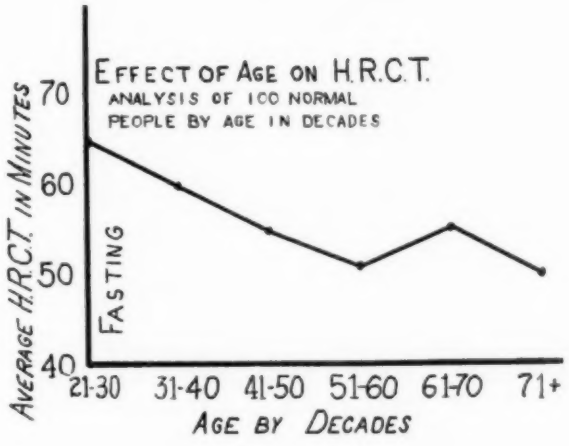

FIGURE 2

two and three hours after breakfast. Patients with the highest values for fasting HRCT showed the greatest drop after a normal breakfast. In a 23-year-old female, the fasting HRCT of 96 minutes fell to 52 minutes—almost a 50 per cent decrease. Age did not appear to play any part in the decrease in HRCT following food intake. Some patients exhibited little or no fall at the end of two hours but a fairly marked decrease at the end of three hours. There has been much discussion as to the length of time required for fat digestion and absorption. Our observations indicate that it varies widely and must be considered on an individual basis. The average total fall in HRCT was 27 minutes, or 37 per cent of the fasting value.

Figure 4 shows the effect of 450 calories of cream on HRCT. There was a definite decrease in all but 1 patient, but there was also a variation between subjects. The fall was more marked at the end of three hours than at the end of two hours. The average total reduction in HRCT was 19 minutes, or 30 per cent of the fasting value.

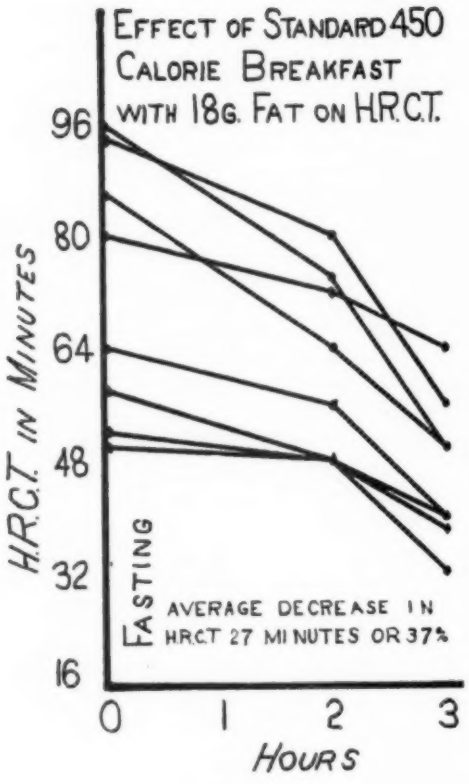

FIGURE 3

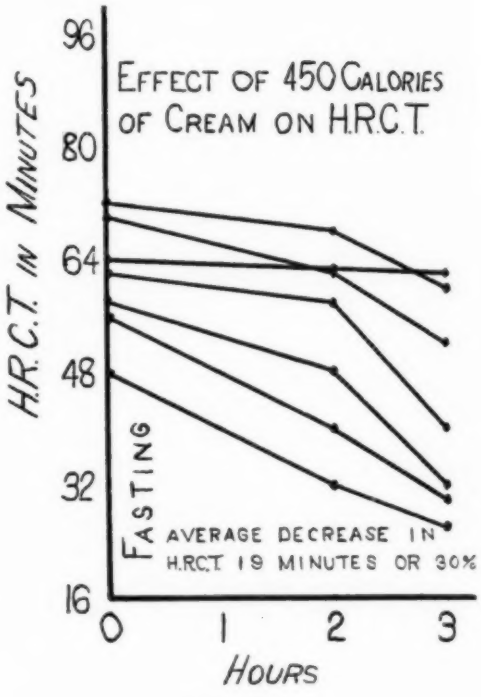

FIGURE 4

Figure 5 shows the effect of 450 calories of corn oil on HRCT. There was some variation in HRCT at two, three and five hours, perhaps due to the different rates of absorption of fat in different patients. The average total fall in HRCT was 8 minutes, or 13 per cent, as compared to 37 per cent after a standard hospital breakfast.

Figure 6 shows the effect of 450 calories of safflower oil[1] on HRCT. The average maximum fall in HRCT was 10 minutes or 16 per cent, as compared to 13 per cent after the corn oil alone and 37 per cent after a standard hospital breakfast.

Figure 7 shows the effect of a standard breakfast of 450 calories with 18 grams of fat plus 450 calories of safflower oil. The average decrease in the HRCT was 13 minutes, or 18 per cent. In the same 8 patients who received the standard 450 calorie breakfast with 18 grams of fat, the average fall was 27 minutes, or 37 per cent; in other words, the fall in HRCT after the average breakfast without the addition of the safflower oil was 100 per cent greater than when the safflower oil was added to the meal. Thus it appears that the unsaturated fatty acids may prevent the marked decrease in HRCT that occurs after the ingestion of food containing saturated fatty acids. In some patients the greatest fall occurred after three hours, and in others after five hours.

Figure 8 shows the effect of a standard breakfast of 450 calories with 18 grams

[1] Kindly furnished by Abbott Laboratories, North Chicago, Illinois.

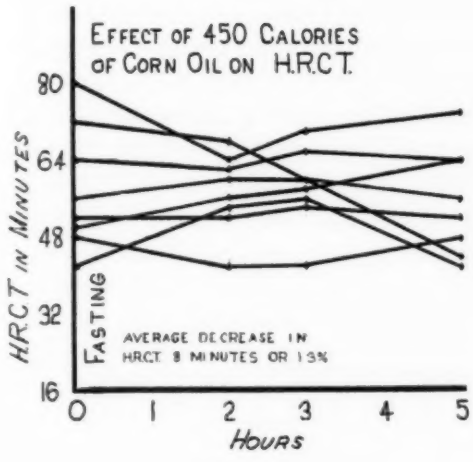

FIGURE 5

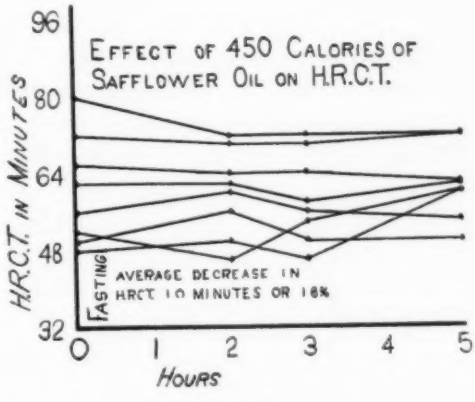

FIGURE 6

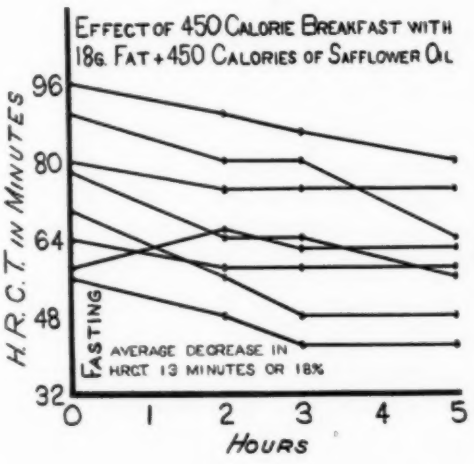

FIGURE 7

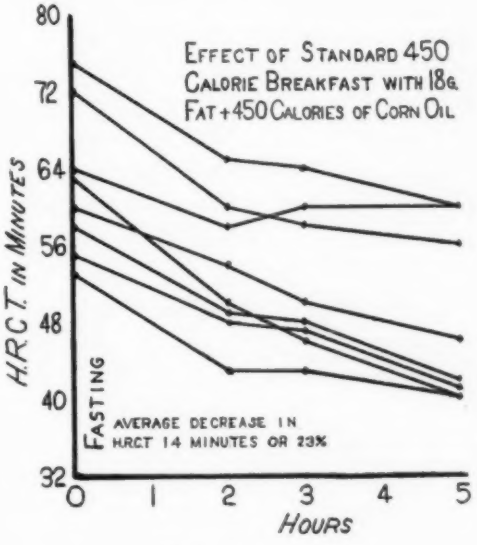

FIGURE 8

of fat, plus 450 calories of corn oil. The average total fall in HRCT was 14 minutes, or 23 per cent, as compared to a 37 per cent fall with a standard breakfast. After 450 calories of corn oil taken alone the average fall in HRCT was 13 per cent, whereas after 450 calories of safflower oil alone the average fall was 16 per cent. When the two oils were given with a standard breakfast containing 18 grams of fat, the positions were reversed. With the 450 calories of safflower oil and a standard breakfast the average fall in HRCT was 18 per cent, but with 450 calories of corn oil and the same breakfast the average fall was 23 per cent.

DISCUSSION

Most of the previous work on postprandial acceleration of clotting has been done by measuring changes in the silicone-tube clotting time and stypven time.

Silicone resembles vascular endothelium in that it does not absorb platelets. Since the platelets are fairly stable, there is little tendency for them to rupture and release the platelet factor (a phospholipid) necessary for the conversion of plasma thromboplastinogen to thromboplastin. The clotting time in silicone tubes is, therefore, several times longer than in glass, where the tube surface causes adhesion of the platelets and release of the platelet factor. It has been repeatedly demonstrated that hyperlipemic blood does not clot more quickly than normal in the presence of a normal number of adequately functioning platelets; however, in the absence of platelets or when their function is interfered with, hypercoagulability becomes evident (7). Our results show that when a standard amount of heparin is added to blood, clotting time is reduced after a meal consisting of saturated fats. This would be expected in the light of present concepts of clotting.

In the clotting process, once a small amount of thrombin has been formed, it exerts a very powerful catalytic action in the conversion of the thromboplastinogen complex into thromboplastin in the presence of platelets. The effect of inactivation of thrombin would be stabilization of the platelets. The main action of heparin on the clotting elements is its powerful anti-thrombin effect (8). One would, therefore, expect the HRCT to behave very much like the silicone-tube clotting time in response to hyperlipemia, and this we have found to be true.

O'Brien has advanced the hypothesis that it is the rise in the plasma level of phospholipid postprandially that accounts for the increased coagulability (7). There appears to be a postprandial increase in "active" phospholipid, *i.e.*, a phospholipid capable of substituting for the platelet factor which is also a phospholipid. Thus, in clotting tests that minimize the role of platelets either by removal or stabilization, a small increment in this "active" phospholipid will produce a significant increase in the speed of clotting.

Our results seem to indicate that saturated fatty acids are the most active of all in the acceleration of coagulation as measured by the HRCT, whereas the polyunsaturated fatty acids like corn oil and safflower oil have only a slight or no effect and even seem to protect against the hypercoagulability observed following the standard American breakfast which is rich in saturated fatty acids. If O'Brien's hypothesis be correct, then the rise in the level of plasma "active" phospholipid is a parameter of the amount and degree of unsaturation of the ingested fat. Absorption of fats is still poorly understood, and the interpretation of differences in results may have to await clarification of the behavior of saturated and polyunsaturated fatty acids. It is possible the long-term effect of vegetable fats on blood cholesterol concentration is in some way linked to the observed effects on coagulability.

Cosgriff *et al.* have shown that the administration of large doses of ACTH and cortisone will shorten the HRCT, and our own observations confirm their findings (9). Adlersberg *et al.* also have demonstrated that comparable doses of steroids over long periods will elevate the blood cholesterol level and presumably the phospholipid level (10). It is tempting to draw the conclusion that a high-fat intake and large doses of steroids increase the rate of clotting (as measured by HRCT) in precisely the same manner, namely, by increasing the "active" phospholipid content of the blood plasma.

Almost every physician at one time or another has observed a patient with myocardial infarction who had partaken of a heavy meal immediately preceding the attack. This suggests that, given a patient with atherosclerosis and a narrowed blood-vessel lumen, a rapid lowering of the clotting time (sometimes 50 per cent) might conceivably be the precipitating cause of a clot or thrombus in that vessel. If this be true, it might explain some of the deaths that occur within one to five hours after the ingestion of a heavy meal rich in saturated fatty acids.

COMMENT AND CONCLUSIONS

The heparin-retarded clotting time (HRCT), when determined on blood obtained from 200 ambulatory patients in a fasting basal state, was found to be fairly constant for each subject.

In a series of 47 nonarthritic convalescing patients, the HRCT was usually decreased one to three hours following the intake of fats. The intake of food rich in saturated fatty acids caused a marked decrease in HRCT, whereas the intake of poly-unsaturated fatty acids like safflower oil or corn oil produced only a slight or no decrease. This is suggestive evidence that the addition of poly-unsaturated fatty acids to an average American breakfast provides some protection from the expected postprandial decrease in the HRCT.

The current concept regarding the mechanism of the association of hyperlipemia and hypercoagulability is discussed, and its possible relationship to atherosclerosis and intravascular thrombosis is considered.

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ON THE CONGENERS OF WHISKEY

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In days prior to the widespread utilization of modern biologic techniques, considerable controversy revolved about whether or not there was a difference in action between alcohol and whiskey on the one hand and various types of whiskey on the other. This controversy perhaps reached its peak in 1907 when Charteris and Cathcart (1) published an amusing, albeit sarcastic, article in the British Medical Journal. The article protests that one gentleman (not a pharmacologist) stated in evidence that a difference in action between various types of whiskies could be demonstrated on animals. A pet monkey made drunk on pot-still whiskey "behaved like a gentleman," whereas when intoxicated with another whiskey it behaved like a beast. In order to refute the non-pharmacologists, Charteris and Cathcart prepared three solutions of alcohol and water of equal alcoholic content. The ethanol in two of the solutions was obtained by diluting the two types of whiskey, and the alcohol of the third solution was grain alcohol. An attempt was made by intravenous injection into rabbits to detect any difference in action of the various preparations on the blood pressure measured at the carotid artery. No distinct difference was noticed. At the termination of this and other experiments, the authors concluded that the action of whiskey on pulse and pressure depends upon its alcoholic content and not upon any special body distilled over in the process of manufacture of the whiskies. Friedenwald (2) in the Pathological Laboratory at the Johns Hopkins Hospital in 1911 was outwardly dissatisfied with the limited types of investigation in existence at the time. He tested the acute toxicity of various types of alcoholic beverages on a limited number of animals. Friedenwald, even before his experiments, apparently believed that the general opinion was that fusel oil is far more injurious to health than is ethyl alcohol. In order to achieve experimental verification of this point and also to test the effect of congeners on the toxicity of beverages, he obtained pure alcohol, "inferior whiskey," "genuine whiskey," rum, brandy, gin, benedictine, beer, ale and a miscellaneous group of liqueurs. For purposes of his study he reduced the alcoholic content of each beverage to 38 per cent when the initial concentration of alcohol permitted, or when the concentration did not permit, the alcoholic content was adjusted to 10 or 5 per cent. Series of alcoholic solutions were then administered intravenously to rabbits and a comparison of the toxicities obtained. The end-point of these experiments was the death of the animals. Friedenwald concluded that his observations made it evident that the toxicity of alcoholic beverages was not proportionate to the percentage of alcohol present, but rather proportionate to the amount of other substances which the beverages contained. He believed that liqueurs and rum were the most toxic of the beverages studied. It was inferred that wine is more toxic than whiskey, and that red wines are more

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toxic than white vines. He also concluded that beer and ale are about as toxic as whiskey. Inferior whiskey was rated more toxic than whiskey of good quality.

CONSTITUENTS OF WHISKEY

On the basis of the foregoing and many related data (3–8) it is important to consider the subject of congeners in evaluating both the physiologic and psychologic effects of alcoholic beverages. Snell (9), in a recent article, points out that congeners are substances which appear in all alcoholic beverages along with ethyl alcohol and water. The term congener embraces a variety of substances including fusel oil, tannins, various solids, esters, acids, aldehydes, and a large number of characterized and uncharacterized organic compounds. It is generally believed, in the case of whiskey, that most of the congeners enter the beverages from the grain. Other congeners, notably the tannins, are considered to arise from the wood of the barrel during the process of aging if aging is employed in the manufacture of the beverage. The flavor, bouquet and color of the beverage are influenced beneficially or adversely by the congener content. Since most consumers rarely, if ever, drink straight grain alcohol, the congeners become an important factor in determining the choice of beverage. In addition to credit for desirable qualities, congeners also receive credit for many of the toxic qualities of beverages. Although congeners are diverse and many in nature, it is often thought that only the fusel oil accounts for many of the after-effects and undesirable reactions, such as hangover.

There are no readily available scientific studies which indicate the exact nature and number of congeners to be expected. However, it is not unreasonable to suppose that the total number is in excess of several hundred, and one may confidently expect with the application of modern techniques, such as gas chromatography, paper chromatography, use of the mass spectrometer and infrared spectroscopy, that this number will soon be recorded in the literature.

In addition to advances in congener control which may occur with the appearance of new analytical methods, advances may also be anticipated in the science and art of distillation. This, together with the development and public acceptance of blended whiskies (formed by the judicious admixture of straight and grain whiskies[1]) creates an opportunity for the consumer and experimenter to select a beverage on the basis of content of alcohol, congeners and taste preferences. It now appears desirable to reappraise the physiologic action of congeners and to point out several areas in which additional investigation is desirable.

The customary analysis of distilled beverages concerns itself (9) with the content of ethyl alcohol, fusel oil, total acids, esters, aldehydes, furfural, tannins, and total solids. The esters are usually assayed as a group and the results expressed as grams of ethyl acetate per 100 liters of beverage calculated to 100 proof. The values for aldehyde are customarily expressed as acetaldehyde on the same basis, and similarly the values for total acids are expressed as acetic acid.

[1] Grain whiskies are the light bodied whiskies which are, in the continental United States, usually referred to as grain neutral spirits, since most of the congeners have been removed in the process of high proof distillation.

Fusel oil

In general, the term fusel oil is used to include materials present in whiskey which are undesirable in large amounts and perhaps tolerable in small amounts. Since these materials contribute to the flavor and bouquet, which are important both psychologically and physiologically, they achieve public acceptance. In the scientific literature, the term fusel oil is defined in a variety of ways. There is, furthermore, little agreement concerning the physiologic effects of substances in this category. This, perhaps, is not surprising, since fusel oil varies in composition and is present in varying amounts dependent upon the source and mode of manufacture of the beverage. Snell (9) uses the term fusel oil to embrace the normal and isoamyl alcohols, isobutyl alcohol, and smaller quantities of normal and isopropyl alcohol together with the corresponding esters. The data in Snell's paper illustrate the wide range of congener and fusel oil content in whiskies and the marked reduction thereof in blended whiskies (Table 1). Lockett (10) describes fusel oil as consisting mainly of two alcohols, isobutyl carbinol (inactive amyl alcohol) and active amyl alcohol. He also states that formic acid, acetic, propionic, butyric, valeric and other acids are present, as are ethyl acetate and other esters in small amounts. The picture is further complicated due to the fact that the official method for determining fusel oil is considered (9) "lengthy, troublesome, and scientifically inaccurate." The method is criticized on the basis that isopropyl alcohol, if present, becomes oxidized to acetone in the procedure and therefore is not determined in the official method. In addition, secondary isobutyl alcohol becomes oxidized to the corresponding ketone and is also missed when oxidization is arrested at this point. If oxidization proceeds further, then, two molecules of acetic acid arise instead of one. This leads to high values. The recovery of normal and isoamyl alcohols is reported to be in the neighborhood of 65 to 70 per cent, and the recovery of butyl and propyl alcohols is stated to be even less by this procedure. The advent of new analytical tools should do much

TABLE 1

*Congener Content of 6 Types of Distilled Spirits**

	American Blended Whiskey	Canadian Blended Whiskey	Scotch Blended Whisky	Straight Bourbon Whiskey	Bonded Bourbon Whiskey	Cognac Brandy
Total congeners (wt./vol.%)	0.116	0.085	0.160	0.292	0.309	0.239
	Grams per 100 liters at 100 proof					
Fusel oil	83	58	143	203	195	193
Total acids (as acetic acid)	30	20	15	69	63	36
Esters (as ethyl acetate)	17	14	17	56	43	41
Aldehydes (as acetaldehyde)	2.7	2.9	4.5	6.8	5.4	7.6
Furfural	0.33	0.11	0.11	0.45	0.90	0.67
Tannins	21	18	8	52	48	25
Total solids	112	97	127	180	159	698

* Reprinted by permission from Snell, C. A.: The congener content of alcoholic beverages, *Quart. J. Stud. Alcohol*, **19:** 69–71, 1958 (p. 71).

to bring about the progress which is badly needed in this field, and it is anticipated that satisfactory methods will soon appear. Despite all of these difficulties, much has been done to gain insight into the physiologic and possible physiologic effects of the fusel oils. There seems to be both general and scientific acceptance of the fact that fusel oil in large quantities is undesirable. In addition, there are studies from which it has been concluded that congeners of certain types and in controlled concentration are desirable in beverages and tend not only to improve flavor but also tend to reduce the potential toxicity of the beverage (11).

When fusel oil is isolated from an alcoholic beverage, it is obtained as an oily liquid which has a burning taste and generally a strong aromatic odor. In sufficient quantity it will produce intoxication and narcosis. Poisoning from fusel oil can result in respiratory failure. Fusel oil taken orally is about five times as toxic on a weight basis as ethyl alcohol. The vapors of fusel oil will severely irritate the respiratory tract and produce coughing, dyspnea and headaches. Despite many studies showing the contrary (12, 13), it is still often believed that fusel oil is present in largest amounts in unaged whiskey and that in the aging process it gradually disappears. Several authors have shown that fusel oil does not disappear during aging; in fact, the relative concentration rises. It is presumed that since this material is less volatile than ethyl alcohol, less fusel oil than ethanol is lost by evaporation during the aging process. Control of fusel oil hence is best effected through the initial process of distillation and through blending the finished beverage with grain whiskies or grain neutral spirits.

Ethyl alcohol

After ingestion of the whiskey, the physiologic processes for elimination of ethyl alcohol include metabolism and excretion by way of the lungs and kidneys (14). A variety of metabolic systems are involved. Ethanol and other alcohols are to a minor degree converted to esters of glucuronic acid and excreted as such in the urine (15, 16). The major part of metabolized ethyl alcohol is first converted to acetaldehyde. The acetaldehyde is in turn dehydrogenated or oxidized to yield acetic acid (17, 18). Both of these steps are energy-yielding reactions. Acetaldehyde may also enter into thiazolidene formation with cysteine or similar amino acids; it is also capable of combining with proteins. The precise physiologic significance of many such reactions is not completely understood. Once acetaldehyde has been converted to acetate it can enter a variety of reactions and may be used for synthesis of fatty acids. It can take part in the formation of acetoacetate. Acetate can also serve in the synthesis of cholesterol and related compounds. The major part of metabolized ethanol is eventually excreted as carbon dioxide. Smaller portions such as those which are converted to acetate and in turn converted to cholesterol (19, 20) are turned over at a relatively slow rate in the body. *In vitro* studies have shown that there are two pathways for the oxidation of ethanol to acetaldehyde. The conversion of alcohol to acetaldehyde in mammals is accomplished by the enzyme, alcohol dehydrogenase. This enzyme has been obtained in crystalline form from horse liver (21). Many studies on the enzymatic conversion of alcohol to acetaldehyde in the presence of this enzyme

have been made in the laboratories of Theorell (22, 23). The coenzyme for this reaction is diphosphopyridine nucleotide, and during the course of the reaction, diphosphopyridine nucleotide is converted into reduced diphosphopyridine nucleotide by means of hydrogen derived from the alcohol. The resultant acetaldehyde is then available for other reactions. The enzyme system involved appears to be relatively specific for ethyl alcohol (22). Methyl alcohol, for instance, is not attacked by the enzyme.

Although methyl alcohol does not appear in whiskey, study of it has done much to aid in the investigation of the enzymatic reactions which are important to an understanding of the physiologic effects of whiskey. Since methanol can be converted by the body to the toxic products formaldehyde and formate (24), other enzymatic systems must be sought to explain the oxidation of methanol. Keilin and Hartree in 1945 noted that when ethyl alcohol is treated in a system containing hydrogen peroxide and catalase, acetaldehyde is produced. Catalase in this reaction forms a complex with hydrogen peroxide (25). This complex can react with a variety of primary alcohols including methanol (26). It is probable that the catalase-hydrogen peroxide reaction largely accounts for the oxidation of methanol observed *in vivo*. Higher alcohols such as n-butyl and isoamyl alcohol are oxidized by this same enzymatic system, but the oxidation proceeds at slower rates (27, 28). Secondary alcohols are oxidized to ketones by the catalase-hydrogen peroxide system; indeed ketones can be identified in the blood, urine and expired air of animals after administration of the secondary amyl alcohols (29). Haggard, Miller and Greenberg (29) concluded from the results of administration of secondary alcohols in the rat, that the lethal effects of high dosages were due partly to the ketones formed, and partly to unmetabolized alcohols. Beer and Quastel (30) presented evidence to support the view that ethanol and higher alcohols can inhibit oxidation in brain cells directly and without involving the intermediary metabolism of the alcohols. The higher alcohols were more effective than ethanol in this regard.

In view of the many studies on fusel oil and congeners in which the high toxicity of these materials has been demonstrated, it would seem reasonable to conclude that whiskies will always be more toxic than corresponding doses of ethyl alcohol and water. Experience has shown, however, that this is not the case. Facts again point to the physiologic desirability of congeners in certain instances, provided the nature and quantity of the congeners is under careful control. Haggard, Greenberg and Cohen studied (11) the influence of congeners on the physiologic action of alcohol in some detail. These investigators found that certain samples of commercial ethyl alcohol, which contained smaller amounts of congeners than are found in whiskey, had higher toxicities than did the corresponding amounts of ethyl alcohol in certain samples of whiskey. Recognizing that many of the physiologically active congeners had not been chemically identified, these investigators considered the possibility that some of the congeners affected liver function and were physiologically active in small amounts, perhaps of an order of magnitude as low as that of the vitamins or hormones. In the light of more recent data, it is not unreasonable to suppose that certain congeners may

exert a controlling influence at the enzymatic level on the biochemical reactions into which ethyl alcohol and its oxidation products enter. With the aid of isotopes it should be possible to obtain some of the answers to the various questions which arise in this field.

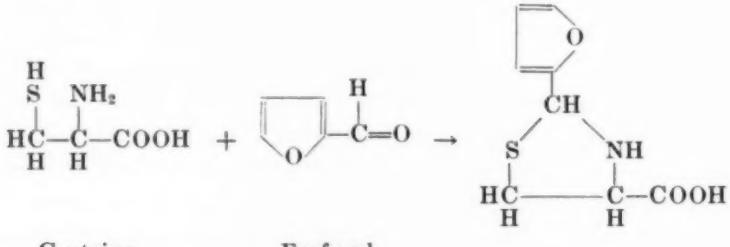
Furfural

Since modern chemical technology can control the fusel oil content of whiskies, it should similarly be possible to control the furfural content of the finished beverage through manufacturing and blending techniques. A great deal of our knowledge of the physiologic action of this compound arises from the petroleum industry, in which furfural is used in large quantities in solvent extraction. In addition, the properties of furfural have been studied by the organic chemist since the early 1800's. Many of the chemical reactions that were studied in early days were primarily of interest to the dye chemist, but much of what seemed then applicable only to dyestuffs seems now equally applicable to biochemical processes of some importance. Generally speaking, the industrial use of furfural is uncomplicated by toxic reactions. There are extreme conditions, however, and some difficulties may develop (31, 32). High concentrations of furfural in the air (0.007 to 0.053 mg. of furfural per liter) may cause headaches, itchiness of the throat and weeping of the eyes. McGuigan (33) concluded that, towards goldfish, furfural is about half as toxic as phenol and approximately one-third as toxic as formaldehyde. Small oral doses of furfural in animals produced stimulation of the central nervous system. Larger doses caused death as a result of central depression and respiratory paralysis. Although the aforementioned and other investigations do much to aid those dealing in industrial medicine with large quantities of furfural —quantities from which acute toxic reactions may be expected—there is a paucity of data on the effects of smaller amounts of furfural and other congeners in association with alcohol alone or in association with alcohol and other congeners.

Furfural vapor is an irritant to mucous membranes. Recent studies using the rabbit eye (34, 35) have shown (36) that aqueous furfural is many more times irritating than ethanol on a weight basis. Paul and associates (37) fed furfural to rats and found that the major urinary end-product was furoylglycine. The same product can be isolated from the urine after feeding furoic acid, furfural diacetate or furfuryl alcohol. It would appear, then, that furfural is changed to furoylglycine by way of furoic acid and that furfuryl alcohol is dehydrogenated in the body to furfural and then further oxidized to furoic acid for conjugation with glycine. Tsunoo and Shiori in 1951 (38) attempted by removal of the spleen of experimental animals to overcome the toxic actions of furfural on the liver. In 1939 Nakahara and Mori (39) published a preliminary note on the production of cirrhotic changes in the liver by the feeding of furfural. These studies were made for the purpose of finding out whether or not any congeners of saki caused the liver damage which is often nutritionally associated with the consumption of alcoholic beverages. Rats were fed a diet of polished rice to which had been added a number of the known constituents of saki. The series included carbohydrates, amines, methanol, ethanol, methyl ethyl ketone, furfural and other

substances. Under the experimental conditions of the series, only furfural produced any pathologic changes. At the onset of the experiment, a dose of 40 cc. of furfural was mixed with 1 Kg. of polished rice. Over a period of two months the dose was increased to 100 cc. of furfural per Kg. of polished rice. During the first thirty-seven days of the experiment a number of the rats died. The livers of these animals showed no pathologic changes, however. The diet was continued in the remaining rats. Their livers exhibited definite pathologic changes, ranging from somewhat localized whitish areas to generalized cirrhotic changes. The maximum time of survival with this high-furfural diet was eighty-eight days. The more extensive report of this investigation was published in 1941 (40). No hepatic changes were produced by acetaldehyde, one of the important metabolic products from ethyl alcohol, or by methanol, propyl alcohol, butyl alcohol, amyl alcohol, glycerol, and methyl ethyl ketone. It was reaffirmed that furfural alone of the ingredients of saki produced cirrhosis of the liver. No pathologic changes were observed in the spleen and other organs.

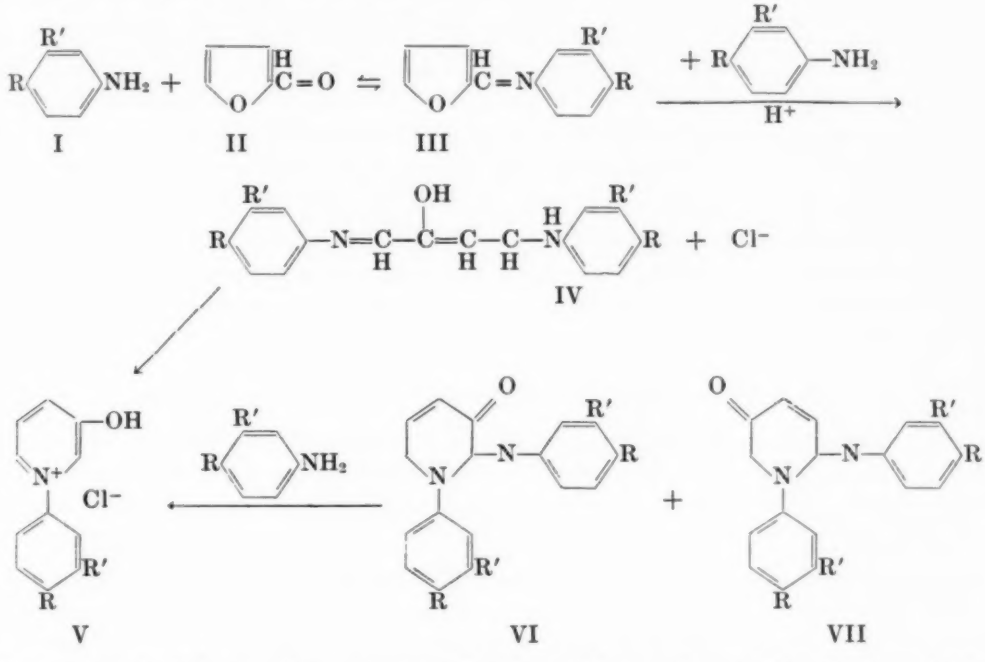
The carbonyl function of furfural on theoretical grounds should enable the molecule to enter the wide variety of chemical reactions which may have profound physiologic significance. For instance, it is easy to visualize a reaction between furfural and cysteine leading to a formation of a thiazolidene, as shown in the following equations:



Cysteine I — Furfural II — III

The thiazolidene (III) shown above is analogous to the thiazolidene formed by reaction of formaldehyde and cysteine which has recently been found to enter into enzymatic reactions involving the transfer of methyl groups or one-carbon fragments in liver preparations (41, 42). Other di- or trimolecular reactions involving the carbonyl group of furfural and NH_2 groups become equally attractive possibilities, both chemically and physiologically. The reaction between furfural and 1 mole of aromatic amine under neutral or acidic conditions leads to the formation of a Schiff base. Many compounds of this type have been well characterized, and the reaction can be employed for the identification of furfural or for the identification of the aromatic amine involved, particularly if the reaction is carried out under neutral or basic conditions. The reaction between furfural and aromatic amine in the presence of acid is much more complex if the aromatic amine is present in excess. Stenhouse in 1870 (43) was the first investigator to describe specifically a molecular reaction under these conditions which leads to the cleavage of the furan nucleus. When the reaction is carried out under controlled

conditions with 2 moles of aromatic amine, 1 mole of hydrochloric acid and 1 mole of furfural, highly colored products are produced, and these are often referred to as Stenhouse dyes. Stenhouse dyes, although cheap and easy to manufacture, have been commercially uninteresting because they are sensitive to both light and alkali. McGowan in 1949 investigated (44) the reaction of the Stenhouse dyes with alkali. On the basis of his work and other studies (45, 46) the following chemical reactions may be expected:



Some steps in this reaction are generally reversible, as shown. The final product, V, is a quaternary ammonium compound. Compounds of this class, sometimes called invert soaps, have usually the ability to reduce surface or interfacial tensions to a high degree. Reactions of the type indicated are interesting also in the production of resins. Under the proper conditions, furfural and aromatic amines can react in the presence of a deficiency of acid to give rise to a material which can even be used to bind soil and aid in its stabilization (47).

More interesting from a biologic point of view are the possible reactions which furfural of the diet may undergo in the stomach with various pharmacologically active aromatic amines. Procaine amide (where R = $COCH_2CH_2N(C_2H_5)_2$ and R^1 = H) and para-aminosalicylic acid (where R = COOH and R^1 = OH) are 2 important pharmacologic agents which have distinct possibilities for entering into reaction with furfural. The reaction between furfural and aromatic amine (2 moles) in the presence of acid proceeds rapidly to the Stenhouse dye. In fact, this reaction is often employed in the quantitative determination of furfural, although some of the substituted furfurals will undergo a similar type of reaction. It can easily be demonstrated in the test tube, by the appearance of color, that procaine amide will, at pH 1 to 2 under conditions simulating those to be found in

the stomach, enter into the Stenhouse reaction with the formation of highly colored products. Further, it can be anticipated that with subsequent alkalinization in the small intestine, reactions of the type described by McGowan will take place. Although never studied *in vivo*, definite possibilities exist for such reactions of furfural with aromatic amines. Such conjectures, though interesting, cannot substitute for many desirable experiments.

General

An examination of the existing literature on the physiologic effects of congeners leads to the lasting impression of marked similarities between the congener problem and other problems in nutrition. In the selection of alcoholic beverages for both experimental use and general consumption, congener balance becomes an important factor. The existing literature points to the fact that this balance can be attained in at least some areas of commercial production of alcoholic beverages. The physiologic studies already cited demonstrate that control of congeners, as achieved through manufacturing and blending techniques which regulate their type and quantity, can lead to either an increase or decrease in toxic effects. For the consumer, the latter is certainly more desirable.

SUMMARY

A review of the technologic aspects of the manufacture of whiskey and certain biochemical aspects of congeners indicates that further advances will be made in bringing the types and number of congeners into proper balance and control. The congeners (which include fusel oil, aldehydes, furfural, esters, solids, tannins, and many uncharacterized compounds) are necessary for the taste, bouquet and color of whiskey, but when present in large amounts enhance the possibility of toxic reactions. The evidence suggests that small quantities of congeners in proper balance, such as found in some types of blended whiskies, may lessen undesirable physiologic effects through interaction with ethanol and other constituents of the beverage. A consideration of these factors points to the desirability of further biochemical and toxicologic investigations, with emphasis on the fundamental mechanisms.

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THE RELATION OF AGE AND SEX TO TELLING LIES

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The question of a woman's age has always been considered to be her inscrutable secret. If ever volunteered, her stated age would invariably be accepted as a fanciful flight from reality. The numerous anecdotes of entertainers and after-dinner speakers bear ample testimony to the common belief that in a comparison of the sexes, the female specializes in prevaricating about her true age. Although quite capable of defending her sex against insults, whether justifiable or not, womankind has accepted with passivity the commonly accepted notion that lying about age is part and parcel of being a female.

Throughout the centuries, however, an injustice may have been done to women by virtue of such allegation. We have, therefore, attempted to evaluate this age-old belief, by making an eight-year survey of the lying propensities of male and female adults in different age groups with regard to their answer to a simple question, namely, "How old are you?" No comparable study could be found in a survey of the medical literature.

METHOD OF STUDY

One hundred and fifty-one male and female adults in 3 age groups (18–25 years, 30–50 years, and over 50 years) were selected for study as representing young, middle-aged and elderly persons. It was felt that this investigation would be valid only if the answer to the question of age were to be elicited from patients who were psychically and organically sound at the time of survey. Any person in acute physical distress, or who subsequently was found to have symptoms of an anxiety nature was eliminated from consideration. The reasons for the office visits of the patients studied were only simple complaints such as coryza, need for immunizations, routine physical examination, or a minor skin eruption. To avoid suspicion of purposeful interrogation, the timing of the question "How old are you", was likewise considered important. Therefore, the inquiry was made at the conclusion of the patient's visit, during a nonchalant insertion of the age on a prescription blank. In the rare instances in which a prescription was not given, the patient's age was nevertheless requested. Patients aged 25 to 30 are neither young nor middle-aged; therefore, they were not included. At the conclusion of a study extending over eight years, some patients would naturally fall into the next higher age group. Statistically, they were considered to belong to their initial classification at the time of the first inquiry about age.

The shortest interval between interrogations for each patient was twelve months, and the longest interval thirty-three months. The minimum number of times a patient was questioned was three times, and the maximum six times.

A lying patient was considered statistically to be any one who deviated from the truth one or more times. It was most important to establish a base-line age at the time of first inquiry. For practical purposes this base-line age in each case had to be accepted as the epitome of truth in order to form a basis for comparison with future answers regarding age; it did not matter whether this base-line age was accurate or not, since the truth or fiction of the statement would be subsequently revealed.

The method of cataloguing age for future inquiry was simple. When the patient left the

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TABLE 1

Tendencies to Lie in Admitting Age, Compared by Sex and Age Groups

	Males			Females		
	18–25 yrs.	30–50 yrs.	Over 50 yrs.	18–25 yrs.	30–50 yrs.	Over 50 yrs.
No. of patients	11	52	14	9	48	17
No. of lying patients	0	7	1	0	5	0
Percentage of lying patients	0	14	7	0	10	0

office a small file card containing the date of interview, stated age, and marital status was attached to the patient's clinical record. At the time of subsequent visits, at least twelve months later, the same information was elicited and recorded on the file card.

RESULTS

The results are shown in Table 1.

Statistics concerning the magnitude and frequency of lying were not deemed practical, since visits were spaced irregularly, according to the whims of the patients, and the number of inquiries would vary in each case. In terms of percentages, therefore, the results would not be as significant as in terms of the incidence of lying in each age group. Suffice it to say that the eccentricities of lying were more evident grossly than statistically, in this sex comparison.

The following conclusions were drawn with respect to lying about age in physically and emotionally competent persons:

I. *Young Age Group* (18–25):

1. No person, male or female, lied about age.

II. *Middle Age Group* (30–50):

1. More males than females lied about their age.
2. One female and 2 males who for years were truthful with regard to age, revised their status to a younger age when they became widowed.

III. *Elderly Age Group* (over 50):

1. Only 1 male and no females lied.
2. The more elderly the patient, male or female, the more prompt was the response with regard to age and the more apparent was the voiced pride in having attained advanced age.

IV: *Middle Age and Elderly* (applicable to both groups):

1. No definite pattern of lying about age could be applied with regard to the patient's marital status.
2. Every instance of a lie in both sexes was directed towards a younger age.
3. Though in general the males lied more frequently than the females, the lies of the females were more incredible and labile.

4. Some patients, male and female, who would lie about age on a given visit might be truthful on subsequent visits as compared to the original baseline statement. However, inquiries at later dates would again reveal a recurring tendency to lie.

SUMMARY

The age-old fable that more females than males lie about age is unfounded in the light of data compiled in an eight-year study on 151 mentally competent patients. Lying occurred more frequently in the middle aged group (30 to 50 years), with the male sex predominating in the overall percentage of liars. An accelerating factor in the precipitation of lying about age seemed to be the assumption of widow- or widowerhood. Whether a patient was single or married did not have any bearing on lying. Though the females lied less frequently than the males, they were the bigger liars.

THE CHANGING TREND OF A GERIATRIC WARD

A Comparative Analysis of the Admission and Discharge Rates of Patients in One Geriatric Ward during 1949 and the First Quarter of 1959

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A marked change took place in the admission and discharge rates of patients in one geriatric ward between the year 1949 and the first three months of 1959, as shown in Tables 1–3. There were several reasons for this increased turnover of patients, but first it will be pertinent to view the picture as it was in 1949.

The ward in 1949

Ten years ago the ward had a bed-complement of 53 and was a component of the hospital annex. The main purpose of the annex was to provide alternative accommodation for patients transferred from the "acute wards" of the main hospital, ostensibly to prevent the blocking of beds for patients with acute diseases by those with chronic diseases. The word chronic is used far too often and implies a negative and despairing attitude towards the patients involved.

The majority of patients admitted to the annex were transfers from the main hospital. They came with no prospects of rehabilitation, though the long periods of time that they survived in the annex stands testimony to the nursing care they received, often under trying conditions. The attitude toward the patient, insofar as treatment was concerned, was passive rather than active.

The environment was institutional, drab and depressing—painted brickwork, old-type of beds crammed together, and furniture that left much to be desired. Unfortunately the local population and medical and nursing staffs at the main hospital had over the years viewed the annex as the next place to hell. Such a stigma is hard to erase, and many well-meaning people had some fantastic ideas as to what this section of the hospital was really like. In fact, even this year, 2 patients were admitted to the ward and their respective wives were inconsolable in their grief at such a disaster. In between tears the good ladies were most definite in their opinion that these patients would not leave the hospital alive. Even the modern surrounding of the up-graded ward failed to inspire confidence. It was the annex. All the stories they had heard over the years were destined to come true. Needless to say their fears were unfounded, for both patients were ultimately discharged home. Both were ambulant; thus they were not returning home in an invalid state. The patients (a stockbroker and a foreign interpreter) and their wives in this instance were educated people.

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TABLE 1

(Total number of beds, 53)

Admissions from January 1 until March 31, 1949	14
Admissions from January 1 until December 31, 1949	35
Discharges from January 1 until March 31, 1949	4
Discharges from January 1 until December 31, 1949	9

TABLE 2

(Total number of beds, 40)

Admissions from January 1 until March 31, 1959	29
Discharges from January 1 until March 31, 1959	10

TABLE 3

Deaths from January 1 until March 31, 1949	2
Deaths from January 1 until December 31, 1949	8
Deaths from January 1 until March 31, 1959	18

The Consultant Physician

In 1949 (within the first year of the National Health Service) there was only 1 doctor to serve this section with a total bed-state of over 300. Any emergencies were dealt with by the duty Medical Officer at the main hospital. When a Consultant Physician was appointed in 1953, a new era commenced for the annex, or Delauneys Hospital as it was officially termed. A large number of ambulant patients were discharged to hostels run by the local authority (the Manchester Corporation) or the Salvation Army. The vacancies were quickly filled and the wards lost many old faces and received many new ones. For the first time Delauneys Hospital could be referred to as a geriatric hospital and not one for the chronic sick.

The up-grading of the wards

During the last five years an intensive building programme for the hospital has brought about a transformation on several of the geriatric wards, including my own, from a dismal workhouse atmosphere to a modern atmosphere with plastered walls suitably painted in bright pastel colors, and with window curtains to enhance the appearance. The addition of a sterilizing room ensured that surgical procedures could be carried out in the correct environment. Each patient was supplied with a locker and a formica-topped metal bed-table.

The present-day programme (1959)

We come now to the programme for determining the admission and discharge of patients at the present time. Prior to the appointment of a Consultant, the majority of patients were transfers from the main hospital. Today the majority are admitted directly from home or a municipal hostel. For example, of the 29 patients admitted to my ward this year, only 3 were transfers from the main hospital. Therefore a remarkable change has taken palce in the source of our admis-

sions. With regard to the direct admissions, our Consultant or his assistant sees and examines the patients in their own homes or hostels, prior to entry. A waiting list is drawn up and the patient-to-be is allocated a place thereon according to priority of circumstances. Here not only the medical position but the social position is considered in assessing the period of waiting; the question of vacancies here at the hospital will also determine the quickness of admission. The discharges and the inevitable deaths create the appropriate vacancies.

The deaths on this ward from January 1 until March 31, 1959, numbered 18—which is very high. Without making excuses, the reasons were that a severe winter had caused a high incidence of disease, especially chronic bronchitis, a contributory factor being the frequent fogs. An influenza epidemic had killed off many old people, not only in hospitals but at home. This led to the distressing situation wherein a prospective patient deteriorated physically following the pre-hospital visit of the Consultant. Thus when a vacancy finally occurred, death often ensued within a few hours or days after admission.

The discharge of patients

The most satisfying moment in a geriatric ward is when a patient leaves for home or a hostel, representing the successful outcome of concentrated teamwork on the part of doctors, nurses, remedial-gymnasts and almoners.

The prospects of discharge depend upon the diagnosis and prognosis. At the beginning, medical examinations, investigations, treatments and nursing care will direct the patient on the right path. The advent of remedial-gymnasts has been the turning point in the rehabilitation of the patients. Without the course of exercises many patients would not have gone home.

I cannot overemphasize the importance of cooperation between the 4 groups of workers in the hospital. Without such teamwork, a geriatric ward will deteriorate to its negative and unhappy past. The remedial-gymnasts have worked out a programme suitable for their own requirements and for the patients. I am indebted to them for permission to quote their programme as it is written.

"When a patient is considered suitable for physiotherapy he then is assessed as a Grade Four. No patient will move from this grade if he is uncooperative. In this group are patients who cannot dress or walk, are unable to wash themselves or sit or stand unsupported. Patients in each grade are reviewed monthly in regard to progress. The first step from Grade Four is to Grade Three. In this group, patients must have sitting balance, and be able to stand or walk with two gymnasts or one gymnast and a walking aid. They should be able to assist with dressing and toilet and cooperate. Grade Two patients must be able to walk with one gymnast or one walking aid under supervision, walk to the toilet supervised and attempt stairs with assistance. The top Grade includes those ready for discharge. These patients dress, stand and walk unaided, go to the toilet unaided, and mount steps aided or unaided, dependent upon the type of case."

When Grade One is reached and the gymnasts are satisfied with the progress, the possibility of discharge is raised for discussion. Then the almoner takes over, home conditions are considered, and a decision is made as to the advisability of discharge to the patient's home or to a hostel.

COMMENT AND SUMMARY

A comparison has been made of the admission and discharge rates for patients in a geriatric ward during two separate periods, ten years apart. Ten years ago, treatment was passive and patients were internal transfers from the wards for treatment of acute diseases.

During the first quarter of 1949 the admission rate per total bed-state was 25 per cent, whereas for the first quarter of 1959 it was 75 per cent. The discharges in 1949 were approximately 8 per cent from January to March, and 16 per cent for the whole year. In the first three months of 1959 the discharges were 25 per cent.

The death-rate showed an increase in the first quarter of 1959, for stated reasons. When both discharges and deaths were added for these three months, the total practically balanced the admissions. It is difficult to make an estimate for the nine months remaining in 1959. The circumstances governing admissions vary in the summer, for many patients are sent in for short periods in order that their relatives can go on holiday. Thus the intake of patients to the geriatric wards is influenced by social expediencies.

We can view the future of the geriatric unit with confidence. The static era of yesterday is gone forever. It is interesting to compare the position of this particular ward at the present time with its position ten years previously (which came within the first year of the National Health Service). The aged sick can be rehabilitated and should not be considered chronically ill. A quicker turn-over of patients can be achieved, provided we keep foremost in mind that there is a possibility of discharge and that the stay in the geriatric ward can be one of progress and not negative apathy if the patient is conditionally favored with a good prognosis.

Addendum

Since this article was written the total number of patients admitted to the ward stands at 90, and 43 patients have been discharged. Of the 6 patients who were admitted for a holiday period, 4 have returned home and 2 remain on the ward. Even allowing for the temporary admissions, the total figures are unprecedented in the history of the Geriatric Unit.

The changing trend is all the more apparent when we consider that in a ward of 40 beds, more than double the bed complement has been achieved with respect to admissions, and more than the total bed complement with respect to discharges. The comparatively high death rate pales into insignificance as a result.

BENIGN PROSTATIC HYPERTROPHY AND CORONARY HEART DISEASE: CORRELATION OR COINCIDENCE?

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Reports about the incidence of coronary heart disease have appeared at frequent intervals in the medical literature over the past several years. In general, these papers have supported the "dietary" etiology of coronary artery disease, though some have included other etiologic factors. Recently interesting data have appeared relating to some of these other factors (1, 2). Rosenman and Friedman (3) have reported on the importance of stress as an etiologic factor, implicating certain socio-economic conditions. Other comments about the influence of stress on human physiology and pathophysiology concern the rise in plasma cholesterol concentration (3), as well as the increase in urinary excretion of aldosterone and 17-hydroxycorticoids observed in students at the time of examinations (4). Mention has also been made of the occurrence of hyperglycemia and glycosuria in military inductees at the time of the initial examination, followed by a return to normal levels after the soldiers have become accustomed to the new environment (5). Lewis *et al.* (6) reported that the height of the plasma cholesterol level is correlated with the height of the blood pressure level.

There are many varieties of stress. During World War II, when famine and terror were the order of the day in many European countries, the incidence of clinical coronary heart disease (7) as well as of peptic ulcer was lower than either before or after the war. The influence of stress on the etiology of peptic ulcer has been generally accepted. We would postulate that in Europe during World War II, stress was experienced on a group basis, in contrast to the individualized stress experienced under "normal" conditions. This arbitrary separation of types of stress can perhaps be supported by the lower incidence of coronary heart disease as well as peptic ulcer among more "primitive" tribes whose members usually live and fight as a group, and among whom individual rights and needs do not have the same significance as in our civilization.

In presenting statistical data gathered by a multitude of investigators, the problem is automatically open for attack. In reviewing the literature on the incidence of coronary heart disease, it is apparent that most studies are based on data from various sources compiled in the usual statistical manner. The data in the preliminary report presented here were obtained in a similar fashion, and we are aware of the fallacies involved.

BENIGN PROSTATIC HYPERTROPHY AND CORONARY HEART DISEASE

In various countries

It is common medical knowledge that benign prostatic hypertrophy (BPH) is relatively rare in the Far East. Since it is also known that coronary heart disease

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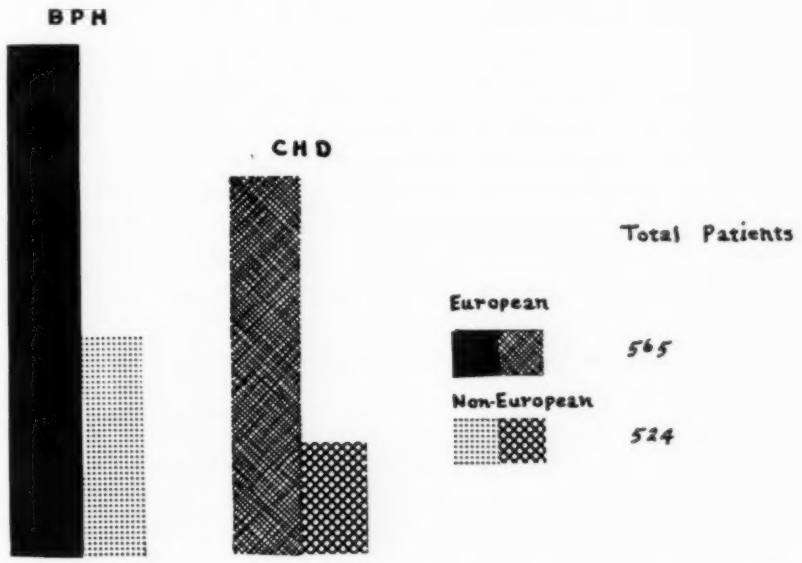

FIG. 1. Of 1089 consecutive patients admitted to the Karl Bremer Hospital, Bellville, South Africa, 565 were Europeans and 524 were non-Europeans, *i.e.* native South Africans. The average age was the same for both groups and the age distribution was similar. Benign prostatic hypertrophy (BPH) was present in 23 patients (4%) of the European group and in 10 patients (2%) of the non-European group. Coronary heart disease (CHD) was present in 17 patients (3%) of the European group and in 5 patients (1%) of the non-European group.

is relatively uncommon in these countries, we have made an effort to evaluate this apparent correlation. Snapper (8) stated that in his experience either BPH or coronary heart disease (CHD) was not often observed among the Chinese seen at Peking Union Medical College, the former condition being a rarity. Data released by the World Health Organization (WHO) show the relatively low incidence of both BPH and CHD in Japan (9, 10). The mortality from BPH per 100,000 population in Japan was 0.2 for the age group 50–54 and 0.6 for the age group 55–59. In sharp contrast are the data pertaining to Denmark; for the same age groups, the figures are respectively 0.8 and 4.3. The same source gives the following figures for the respective mortality rates from CHD: in Japan, 29 (per 100,000 population) for the age group 50–54, and 50 for the age group 55–59; in Denmark, 136 for the age group 50–54, and 260 for the age group 55–59. The data presented graphically in Figure 1 are from the records of the Karl Bremer Hospital, Bellville, Cape of Good Hope, South Africa (11). Scher (12) of the Department of Urology of the Groote Schuur Hospital, Capetown, states that BPH is extremely rare in the Bantu, in sharp contrast to the incidence among the European population of South Africa. These data show that, by statistical analysis as well as by personal observation, both BPH and CHD have lower incidences among the Japanese than among the Danish; and further, that BPH is much more uncommon among the native South Africans than among the European South Africans. The latter observation parallels that made by other authors regarding the incidence of CHD in South Africa.

Etiology of BPH

The etiologic factors in benign prostatic hypertrophy have been considered to be chronic inflammation, arteriosclerosis or "hormonal" imbalance. It has been established that BPH is not a result of sexual activity, as among celibates the incidence is similar to that among non-celibates (13). It appears far-fetched to implicate a direct influence of the diet on the development of BPH, even though starvation will cause libido to disappear. The data presented here show an apparently increasing incidence of BPH with age. However, further review of statistical data on the incidence of BPH reveals a peak in the second half of the sixth decade, with a gradual decline in the incidence thereafter. This would nullify the argument that, since BPH is a disease of aging men, the incidence increases with advancing age in a parallel fashion.

Even though hyperplasia of the prostate gland per se may be under the influence of hormones secreted by interstitial cells of the testes, the testes in turn are under the influence of hormonal factors secreted by the pituitary gland. Stress factors, as well as control over the function of the prostate, appear to be intimately linked to the hypothalamic-pituitary-adrenal axis.

It might be inferred, then, that certain physiochemical changes occurring in men under conditions of stress may play a role in the etiology of both coronary heart disease and benign prostatic hyperplasia.

Comment

We realize that the statements made in this paper are based solely on data gathered from only a few sources. Similar correlations pertaining to other population groups can also be shown. Nonetheless, these observations may indicate only a coincidental correlation—an assumption we do not subscribe to. Further work is needed, either to support or nullify our statements.

To investigate the problem posed, there are several avenues of research. Further statistical analysis may be helpful, but it will not aid materially in coming to a definite conclusion. Clinical studies offer another way in which to shed light on this problem. However, in order to obtain enough data for proper evaluation, a great many investigators would have to cooperate, and this would tend to make the results less accurate and less valid. A third method of study would be the use of certain laboratory tests, which would reflect the presence of clinical coronary heart disease as well as benign prostatic hypertrophy. Even though this might be practical and feasible for the former, it would be prohibitive for the latter, since the necessary information could be obtained only by cystoscopy.

What other tests are at our disposal, aside from autopsy findings? Perhaps the most practical and economical approach would be the determination of certain hormonal substances in the serum and urine of large numbers of men who clinically have both coronary heart disease and benign prostatic hypertrophy. A control group should include men who by the usual means of examination do not appear to suffer from these two conditions.

This method would be feasible for a study of the program posed by us, as well as of other claims regarding the etiology of coronary heart disease, the majority

of which are based on the interpretation of statistical data from a variety of sources.

The prime advantage of the proposed method of study is its applicability to almost every well-equipped laboratory. The error of laboratory data would be relatively small, once the procedure becomes standardized, in contrast with the gross error involved in the much more subjective method of clinical investigation carried on by many observers. It is hoped that in the near future, further study of this subject will be undertaken.

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ANDROGEN-ESTROGEN-THYROID (PLESTRAN) THERAPY IN GERIATRIC PATIENTS

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A few years ago the authors reported favorably on the use of combined androgen-estrogen hormone therapy in the management of the menopausal syndrome and other deficiency states (1). Morrison (2) also has mentioned the efficacy of multihormonal therapy in the aging process. He notes, "Experimental studies in senescent animals have recently shown that multihormone therapy can actually prevent and may even reverse the senescence process under certain conditions."

In addition, a recent investigation (3) in humans has shown that when thyroid is added to such a combination, not only "does the aging involution of some organs cease, but the relative weights and histologic structure of these organs return to levels seen at an earlier age."

Kimble and Steiglitz (4) pointed out that clinically "the incidence of mild hypothyroidism among geriatric patients is far greater than has been generally realized. The disease escapes detection because of a low index of suspicion on the part of the physician, the subtlety of physical signs and symptoms and modification of the clinical picture by the aging process." Among these signs in the age group over 40, they found that chronic fatigue was the most prominent symptom. "Diminished cold tolerance, a tendency to gain weight, dryness and coarseness of the skin and hair, generalized muscular aches, poor memory, palpitation and constipation were frequent complaints. Abnormal physical findings were occasionally entirely absent but when present included the following: dry, brittle hair; doughy skin; poor muscle tone; and a low blood pressure or frank hypotension. Blood pressure and body weight, however, were not accurate guides to the presence or severity of hypothyroidism."

Combined androgen-estrogen-thyroid therapy, therefore, could contribute to peripheral vascular relaxation, a decrease in tissue atrophy, and improved muscle tone through the anabolic action of testosterone on protein metabolism.

Recently we had an opportunity to investigate the effectiveness of such a combination of androgen, estrogen and thyroid (Plestran[1]) in 200 patients in the middle and older age groups. Each tablet of Plestran contains ethinyl estradiol, 0.005 mg.; methyltestosterone, 2.5 mg.; and Proloid, 16.0 mg.

CLINICAL MATERIAL AND METHODS

Forty-eight males and 152 females were studied. The range of age in the males was from 36 to 85 years and in the females from 34 to 91 years. The older patients in both groups were

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[1] Plestran was supplied through the courtesy of Warner-Chilcott Laboratories, Morris Plains, New Jersey.

significantly more numerous. They came from groups seen in private practice, the endocrine clinic, and the medical service of the Ellis Hospital and the Schenectady County Home.

Nearly every patient was interviewed six times during the course of this study. All interviews were conducted by the professional staff of the institutions concerned. By this means, considerable rapport developed between the patients and the investigators.

A careful pre-treatment history and physical examination on each patient provided a base-line by which symptoms were graded from most severe (3+) to least severe (1+). Clinical improvement was graded according to a numerical scale 0,1,2 and 3. Thus the improvement of a patient who changed from 3+ severity of symptoms to numerical 3 in degree of benefit (a gain of 6 points) was called excellent. A numerical gain of 5 was considered very good and a gain of 4, good improvement.

The following subjective complaints were used in establishing the base-line: fatigue, poor mental outlook, forgetfulness, irritability, appetite, generalized aches and pains, digestive disturbances, and (in a few cases) changes in libido. However, because of the advanced age of most of the patients, increase in libido was discarded as a criterion of improvement in the final evaluation.

Many of these subjects were receiving other medication such as digitalis, nutritive supplements or occasional diuretics at the time the base-line data were obtained.

Of the 200 patients, 187 received 1 tablet of Plestran daily for four to thirty-five weeks; 12 received 2 tablets daily, and 1 received 3 tablets daily for a few weeks. The preliminary

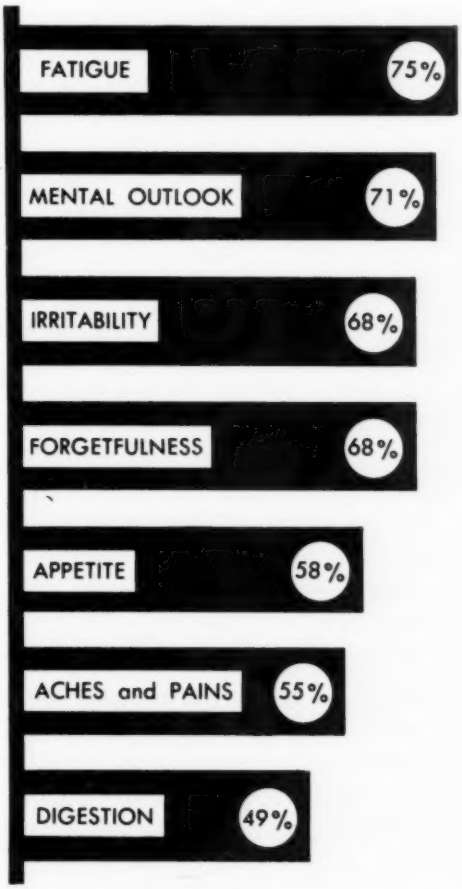

FIG. 1. Percentage improvement with Plestran

conclusion was that if the study had been prolonged, larger doses might have been employed to better effect.

In a somewhat similar study, Birnberg and Kurzrock (5) found that androgen-estrogen therapy was associated with a significant decrease in blood pressure. Consequently, we followed the blood pressure closely, measuring it every time a patient was interviewed. In over 65 percent of our cases, the systolic and diastolic blood pressures were significantly reduced from pre-treatment levels.

No side-effects were observed except in 3 patients in whom digestive upset and diarrhea required withdrawal of the medication. There were no cases of vaginal bleeding. Routine laboratory studies showed no ill effects on the renal or hematologic systems.

RESULTS

With Plestran therapy, from 49 to 75 per cent of the patients showed a gratifying improvement, depending upon the original specific complaint. Excellent to good results (a gain of 6 to 4 numerical points) were achieved in 150 patients complaining of fatigue; mental outlook improved in 142 patients and forgetfulness in 136. Irritability decreased in 136, and generalized aches and pains were relieved in 110. Improvements of similar magnitude in appetite and digestion were obtained in 116 and 98 patients respectively. Figure 1 represents graphically the percentage improvement obtained during Plestran therapy in the subjective complaints within the range of good to excellent results.

COMMENT

Administration of Plestran resulted in gratifying alleviation of such complaints as fatigue, poor mental outlook, irritability, forgetfulness, anorexia, aches and pains, and digestive disturbances. Although subjective complaints are subject to individual variation, it was evident the majority of these patients were benefited clinically by the course of therapy. Undoubtedly, in a number of cases a still greater benefit would have resulted had the original dosage been larger. Moreover, the anabolic effect of the androgen-estrogen combination appeared to be distinctly enhanced by the addition of thyroid hormone.

SUMMARY

A combination of estrogen, androgen and thyroid (Plestran) was administered orally to 200 geriatric patients in an effort to relieve their chief complaints of fatigue, poor mental outlook, forgetfulness, irritability, muscular aches and pains, poor appetite, and digestive disturbances.

The results were most gratifying; from 49 to 75 per cent of the patients showed a good or excellent response in one or more of the categories evaluated.

No untoward side-effects were noted during the thirty-five weeks of therapy. In only 3 of the 200 cases studied was it necessary to discontinue medication because the patient felt worse.

In short, androgen-estrogen-thyroid (Plestran) therapy proved to be effective in alleviating the common complaints of geriatric patients.

Acknowledgment

We wish to thank Dr. Joseph Naumoff and Miss Loretta Youman for allowing us to treat patients at the Schenectady County Home.

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MÉNIÈRE'S DISEASE: A NEW THERAPEUTIC APPROACH

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The conventional therapy of Ménière's disease, a most distressing disorder which leads to total deafness, cannot be considered specific nor overly successful. On the basis of theoretical considerations, we treated 2 cases of Ménière's disease with corticosteroids and obtained remarkable results. In one of these patients, in whom there also developed an alarming bradycardia and heart block, treatment with corticosteroids led not only to complete recovery from Ménière's syndrome but, surprisingly, to the disappearance of the cardiac signs and electrocardiographic changes.

MÉNIÈRE'S DISEASE

Although Ménière's disease is a well known clinical entity, the mechanism that produces it has not been clarified. The chief symptoms are sudden attacks of deafness, tinnitus and vertigo, roaring in one or both ears accompanied by nausea and vomiting, pallor, cold sweat, occasional diplopia, nystagmus, and rarely diarrhea. Equilibrium is disturbed. The attacks last as long as several hours. Headache is pronounced during the attack and persists after vertigo and tinnitus have subsided. The quality of the headaches is pulsatile or aching, similar to that of other vascular headaches. A sensation of headache due to contraction of the cervical and occipital muscles may also occur.

The forms of treatment applied heretofore are:

1. The Furstenberg regimen (1) consisting of a low-sodium diet with restriction of fluids and administration of 8 Gm. of ammonium chloride daily.
2. Atropine sulfate or scopolamine hydrobromide, by injection, for the acute attack.
3. Vasodilators such as nicotinic acid (2) or beta-pyridylcarbinol (Roniacol).
4 Meclizine (Bonamine) or dimenhydrinate.
5. Desensitization (3) with histamine diphosphate or procaine hydrochloride intravenously.
6. As a last resort, aural surgery. The operation consists of destructive labyrinthotomy, resulting in a totally deaf ear.
7. Surgery of the sympathetic nervous system. Johnson *et al.* (4) claim arrest of the pathologic process by this means. According to their report, a procaine block of the stellate ganglion will stop an attack of vertigo instantly and will often stop the tinnitus or improve hearing temporarily. The effect of procaine can be made permanent by performing a dorsal sympathectomy. These authors report not only elimination of the attacks, but also improvement in hearing.

The synonyms of Ménière's disease, such as acute vestibular irritation, aural

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vertigo or labyrinthine apoplexy suggest as an underlying cause an irritation of the vestibular centers or the labyrinth. The process may be degenerative or inflammatory in nature. Cardiovascular disease including arteriosclerosis, vasomotor disturbances and allergy (physical or intrinsic in nature) produces an increase in labyrinthine pressure and dilation of the endolymphatic system (labyrinthine hydrops (4)) which generates the symptoms. The hydrops of the inner ear suggests that a neurovascular disturbance plays a decisive role. Other possible factors are disturbances of the autonomic nervous system.

Faced with the problem of classic Ménière's syndrome in 2 cases, and keeping in mind that allergic reactions are the suspected cause of the disease, it seemed reasonable by analogy with other allergic conditions to try treatment with corticosteroids. A review of the literature did not reveal that the disease had been treated before in this manner. The results were dramatic.

CASE REPORTS

Case 1

J. M., a 64-year-old physician, had suffered from attacks of dizziness, starting twenty years previously. The diagnosis of Ménière's disease had been made at that time. In December 1957, he had an attack of dizziness and vomiting, and a similar attack in February 1958. When first seen on February 21, 1958, physical examination, fluoroscopy of the chest and urinalysis yielded normal findings. Blood pressure was 130/80 mm. Hg. The electrocardiogram showed a slightly widened QRS complex (0.12 sec.). In the subsequent months the attacks of dizziness, vomiting and bilateral deafness became more frequent. Repeated physical examinations did not show any change except the development of bradycardia. On June 30, 1958, the ventricular rate was 35. The electrocardiogram revealed a prolonged P-R interval (0.24), an atrioventricular block 2:1, and a right bundle-branch block. Treatment with Peritrate, Bellergal, aminophylline and Diuril was ineffective. On September 8, 1958, the heart rate was 26. Isuprel, 10 mg. sublingually, was given twice without affecting the heart rate. Following a subcutaneous injection of 0.5 cc. of epinephrine (1:1000) there was a rise of the heart rate to 60. A few days later the heart rate fell again to between 28 and 32. Dizziness, vomiting and partial loss of hearing occurred frequently. The patient became very weak and was bedridden. All treatment failed. On November 28, oral administration of the anti-inflammatory steroid, dexamethasone (Decadron, Merck Sharp & Dohme), was started in a dosage of 0.75 mg. three times daily. The improvement was striking. Vomiting, dizziness and loss of hearing disappeared within twenty-four hours and have not recurred to date. Examination on December 5, 1958, showed a ventricular rate of 64; an electrocardiogram obtained on the same day revealed that the atrioventricular block had disappeared. The dosage of the drug was reduced by decrements. The patient feels well and is able to work. He receives a maintenance dosage of 0.25 mg. of Decadron three times daily.

Case 2

Mrs. K. J. was 34 years old. Her family and past histories were noncontributory. The attacks had came on suddenly two months prior to the examination. They consisted of deafness of the right ear, nausea, vomiting, tinnitus, dizziness and severe headaches. The findings obtained by physical examination, fluoroscopy of the chest, blood studies, urinalysis and neurologic examination, were completely negative. Decadron, 0.75 mg. three times daily, stopped the attacks immediately and restored hearing. The patient returned to full activity without further complaints. She receives a maintenance dosage of 0.25 mg. of Decadron three times daily.

SUMMARY AND CONCLUSIONS

Conventional types of treatment of Ménière's syndrome are reviewed. Their value is limited and doubtful. A new approach using corticosteroid therapy (dexamethasone) has been made in 2 cases, producing dramatic relief of the symptoms and rehabilitation of the patients. These striking results warrant further trial of this method of treatment.

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STIMULANT THERAPY WITH DEANOL IN DEPRESSION, MIGRAINE, AND TENSION HEADACHES

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Chemotherapy may soon be as important in the treatment of mental disorders as it is in the treatment of infections. Deanol (Deaner®),[1] a recently marketed stimulant of unique nature, has been reported to be of value in mild depression, migraine, and tension headaches and to induce a more affable mood (1–3). In 77 private patients with these complaints we have used deanol therapy and found it to be a safe and useful drug.

CLINICAL MATERIAL AND METHODS

Patients. Seventy-seven patients between 37 and 81 years of age were treated. There were 42 females and 35 males. Thirty-eight patients were institutionalized for a variety of physical and emotional reasons, and the remainder were drawn from private practice.

The majority of the institutionalized group suffered from depression of the chronic involutional type characterized by withdrawal from social contact, inactivity, hypochondria, anorexia (or polyphagia), disturbed sleep and poor bowel habits. Acute reactive depression associated with situational stress or the menopause characterized the patients seen in the office; 12 of these had longstanding histories of recurrent migraine or tension headaches.

Previous medication. Of the 38 institutionalized patients, 18 had received long-term iproniazid (Marsilid) therapy with excellent results in 11, good results in 6 and negative results in 1. This agent was withdrawn ten to fourteen days prior to administration of deanol. Others had received various stimulants for several years with no measure of success. Inconsistent and unpredictable results with ergotamine preparations were observed in the patients with headaches.

Laboratory data. Urinalyses, hemograms and tests of renal and hepatic function were obtained before treatment and at six-week intervals or less.

Dosage of deanol. Initially most patients received 25 mg. of deanol daily in the morning. This dosage was repeated once or twice during the day when no response was forthcoming from the single daily dose. More severe cases were treated with higher dosages, up to 125 mg. per day.

RESULTS

The distribution of the clinical results is shown in Table 1.

Effects usually became apparent within ten days and lasted for the duration of treatment. Withdrawal resulted in relapse in most instances.

The response was considered "excellent" when a marked increase in energy, alertness and interest in the environment became evident along with a diminution of symptoms. A "good" response was considered as improvement in the foregoing areas, but to a lesser degree.

Deanol appeared highly effective in relieving acute reactive depression. The

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[1] Deaner® (Riker Laboratories, Inc., Northridge, Calif.) is the para-acetamidobenzoic acid salt of 2-dimethylaminoethanol.

TABLE 1

Diagnostic Classification	No. of Patients	Response to Deanol Therapy		
		Excellent	Good	Poor
Acute reactive depression (menopausal, situational)	21	10	5	6
Chronic depression (somatopsychic, situational)	26	4	12	10
Involutional depression (senile, arteriosclerotic)	18	5	5	8
Headache (migraine, tension)	12	8	2	2
Total	77	27	24	26

response was excellent in approximately 75 per cent of the patients; 83 per cent of those with headache reported good to excellent relief of symptoms.

Toxicity. Studies of blood, urine, renal function and hepatic function disclosed no drug-induced abnormalities, even after administration of deanol for three to six months.

Side-effects were few and not serious. Transitory constipation occurred in 12 cases and was readily relieved with mild cathartics. Three patients reported muscular soreness, and 2 reported nuchal headache. A coincidental complaint in 1 patient was pruritus ani.

DISCUSSION

It has been suggested (4) that some mental and emotional derangements are due to disturbances in acetylcholine metabolism. Acetylcholine has been postulated as important in the correct functioning of the central nervous system (4–6). Deanol may be an intracellular precursor of acetylcholine or a similar substance (5, 8).

Acetylcholine and other quaternary nitrogen compounds have limited ability to cross the blood-brain barrier, whereas deanol crosses this barrier with ease (8–10).

Oral administration in rats lowers the convulsive threshold to audiogenic, electrical and pentylenetrazol-induced seizures (3). In schizophrenic patients, increased motor activity and verbal responsiveness have been reported (3, 13). In children with learning or behavior problems, increased ability to learn and improvement in behavior have been noted (14).

In all laboratory and clinical studies the toxicity of deanol has been reported to be unusually low.

In agreement with the findings of others, we found deanol (Deaner) to be safe, even in elderly subjects (22 of our patients were over the age of 70). Trial of this useful drug in patients of all ages who seem to be suitable candidates may be undertaken without fear.

It seems probable that deanol is most effective in mild depression, and the more potent iproniazid should be reserved for the severely depressed, institutionalized patient.

CONCLUSION

Deanol (Deaner) is a safe and valuable agent in the treatment of depression, migraine, and tension headaches.

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GERIATRICS UNLIMITED*

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In this title, the adjective "unlimited" as applied to the field of geriatrics refers not only to what the State can do for the old person, but also what the old person can reflect back to the community in the form of spiritual inspiration, skills learned over a lifetime, advice of a seasoned nature, and contribution to the economy.

SHORT CLOVER

One day during the bank holiday of 1933, I was called to the home of an elderly woman. It was noon time. There were 5 lard cans turned upsidedown around the lunch table to serve as chairs. The 5 grandchildren who had been wished upon her by her "drifting children" were called to a meal of skim milk, hominy grits and dandelion greens. Blessings were said, and cheerfulness pervaded the meal. After licking of fingers and washing of cheeks, she placed the hands of blessing on the little upturned faces, and all scattered off to school.

I said "I don't get it. How can you, a charwoman in a depression, take on all this responsibility with such good grace?" "Oh," she replied, "you see, I just thank the Lord every day for letting me thrive on short clover."

To me, she reflects the glory of the aged one who not only meets the challenge late in life, but offers a positive contribution to the welfare of others.

OLD LADY DOCTOR

At this juncture it is fitting that I should present the background of a woman doctor who practiced medicine several generations ago. She enjoyed the pioneer examples of John Morgan and Benjamin Rush, but had not yet been exposed to the advent of anesthesia. (Much serious practice was accomplished before the refinements of Pasteur, Koch and Lister.) Such was my maternal great-great-grandmother, Dr. Harriet John, who "read" medicine for two years and then served as medical apprentice for an equivalent time. In her library was the first surgical text written in America by John Jones in 1775. The great State of Ohio, barely a decade old, then granted her the right to practice long before women were accepted in medical schools, and before the stethoscope had reached America. She was old in the practice before the first academically trained woman physician was graduated from Geneva Medical College on January 23, 1849, in the person of Elizabeth Blackwell.

My maternal grandmother became, for a time, the understudy in this heroic

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set-up. Calls were made on horseback. Roads were rough trails. Ohio was just emerging from the wilderness.

In the early 1840's the railroads came through the Northwest Territory. My grandmother described to me an accident at a railroad crossing near Xenia, Ohio. This was a year or so before the introduction of anesthesia in 1846. As the two women arrived upon the scene, they found that a corn wagon had been smashed. The farmer was lying upon the ground with a mangled leg, and his sorrel mare also had a fractured leg. Dr. John ordered the onlookers to suspend the mare's belly in a burlap hammock between two walnut trees and to excavate the ground under the injured leg; gravity served as traction. Meanwhile she was at the side of the human victim. An improvised tourniquet controlled the hemorrhage. She doused the man inside and out with corn whiskey. Her instruments were run through the flame of a lantern, and rinsed in whiskey. Then she performed the amputation. Later the two women fashioned a wooden leg out of a seasoned piece of linden. By next spring, the rehabilitated farmer and his mare were plowing the corn rows.

As an old lady, still doing her stint for more than two generations, Dr. John began to hear of the new wonders in the world of medicine. She adopted ether anesthesia wholeheartedly. The name of Pasteur began to sift through the maze, but she nibbled lightly only, and left these great new developments to others. Dr. Bettmann wonders how such a practitioner would measure up against the modern freshman medical student; he votes, however, for "the intuitive discernment, all-inclusive medical wisdom and human understanding of the old ones." Dr. John lives on today in the personality of the generalist-geriatrician, who with goodness, mercy and intellect reincarnates and reglorifies the medical masters of the ages.

FOOD, SHELTER, RAIMENT AND HANDOUTS

Most energetic lecturing gerontologists from continental Europe are carried away with ideas of food, shelter, raiment, services and handouts when referring to the aged.

In contrast, I can recall my experiences in the summer of 1916, when a companion and I hiked for ten days through Yellowstone Park. On our backs were packs containing blankets, tarpaulin, dried food, musette bag, camera, film, cocoa bucket, pie tin, frying pan and so forth. In the evening we bedded down on a mattress of balsam boughs and moss, covered with blankets topped by a tarpaulin. In the morning we made golden brown muffins from our supply of ingredients, in an oven concocted from the frying pan and the pie tin. We felt quite smug about our accomplishments. Then one day we overtook "The Chicago Hiking Club," consisting of about threescore people of various ages. There were wagons to house the supplies, shelter the unfit, bolster up the timid, and bed down the ill. Heading the bold hikers was the grandpa of them all, cajoling, lecturing, cooking, and explaining the ways of nature to the uninitiated. He inspected our set-up and then exposed us to his methods. Everything we did, he did just a little better. We learned much from that old man. What was bragging

for him, was a golden handout crumb for us. He was a successful retiree who lived for others.

I do not think of social security benefits and industrial pensions as handouts, but as entities opposed to welfare grants. They are income of a solid nature, earned by effort and by the dignity of labor in the heyday of productivity, and through the generosity of employers and the far-seeing policy of government. Whenever retired older people can add a part-time job to their income, I rejoice with them.

One of my male patients retired from an office accounting job at the age of 70. His social security income amounts to $108.50 per month. His pension is roughly equivalent to 40 per cent of his average income for the previous ten years, yielding $160.00 per month. Now, after recovering from a lesser stroke, he has accepted a policeman's job in a school district. There are three short shifts, occupying about half of his time. This nets him $100.00 per month. He has some income from savings and property investment. He and his wife take in a few jobs of fancy laundry. I only wish you could see this happy man in his seventies. His eyes are clear, his blood pressure is controlled, and he has regained his accuracy of speech. Already he has saved the life of a child by quick thinking and action when an automobile driver demanded his right-of-way. The handouts here are in reverse.

This man's job as a retiree is in no way related to his former means of earning a living, and is a demonstration that new skills can be learned, and that one can teach an old dog new tricks.

"CONGENING"

I know an elderly couple with only limited education. He is a retired fraternity porter and she is a retired sorority cook. Both have recovered from old-age illnesses, and both earn a part-time living in their later years. He restores old furniture for an antique shop. She is the professional baby sitter for an entire neighborhood.

One day I was called to their home. A large solarium and television room had been added since my last visit. "The master" approached a cupboard at one end of the room; out came a hook and cross-member with 5 clothes lines attached, which could be stretched to fasten on a bar at the other end of the room. Moreover, an electric washing machine popped out of its hiding place, as well as a mangle. After the laundry phase was over, everything fitted back into its hidden nook, and the television show was on. Out in back, in the hillside, was a root cellar fitted with a carved front and stained glass inserts which lent a cathedral-like appearance.

I said "It's such a pleasure to come here. Old age holds no drawbacks for you." His reply was "Why, thank you, Doctor. In fifty years of married life, the little lady and I are now congening together best of all!"

GENEROSITY OF TALENTS

In recent weeks I have been much inspired by the news that Du Pont retired executives and Wilmington's has-been professional men are pooling their generos-

ity and talents. About 50 of these men have formed a corporation of design, function, consultation, advice and shared experience.

Let us consider a small business that is newly created. The product is good, but the financing is shaky, the production schedules are topsy-turvy, the organization is not clearly defined, responsibilities for departments overlap, and inspection is in a state of smog. Then a Du Pont retiree appears upon the scene. He feels that "after the Middle Ages comes the Renaissance." He makes a survey, blue prints production schedules, takes the snags out of inspection, relates men, materials and dollars in a new economy, and remains long enough to witness a series of payrolls and the approach to a dividend. After the smoke has cleared, what are the compensations? The consultants render their bill of zero dollars, and they move on to newer fields of endeavor, leaving behind lasting gratitude and the genes of their wisdom to serve as leaven in a new, stable industry.

RETIREMENT PLANS FOR THE INTELLIGENTSIA

Into my office there came one day a tempestuous professor about to retire. He was in a state of panic. One would have thought that this situation had been suddenly thrust upon him. There had been no preparation on his part for his retirement program, such as is now becoming the vogue in some industries, starting months or years prior to the event. My patient's heart rate was elevated and he was exhibiting all of the objective symptoms of a "hot flash."

Inquiry revealed an ambitious financial and family program that could not endure with a retirement income. I reached for the telephone and called a friend in a distant city, who operated a teacher's agency. Long-distance introductions followed. A series of interviews became stimulating. A good teaching job in a small college resulted. The new salary plus the retirement income exceeded the amount from the old contract. Rent from his locally owned residence covers domiciliary expenses in the new town. Three years have passed by. The man is remade.

MINIMUM LIVING

Somewhere above the indigent level there is a plateau where existence is tolerated or even enjoyed by retirees on a conservative basis. I have made many inquiries and have done much investigating of old peoples' affairs, and have found that renters and home owners constitute two rough divisions. The renter of a cottage or apartment prefers a minimum space consisting of a living room, kitchen, bedroom, bath and dining nook.

One successful elderly couple rented out two thirds of their home to three college couples, leaving for themselves a large living room with a folding bed, an alcove containing a hot plate and sink, a breakfast nook, and a tiny bath. Their total net income did not exceed $3450.00 a year from rent, social security and odd garden and baby sitting jobs. A roof was over their heads, and the home, as an investment, earned water and heat expense but not the electric bill. A tiny garden yielded vegetables and exercise. They had no hospitalization in-

surance, but the son in a distant city promised this luxury, which they accepted with embarrassment. A typical supper consisted of poached egg on whole wheat toast, onion and lettuce salad, buttermilk and half an orange. No garments had been purchased for years, but a sheet was drawn over a wardrobe of respectable clothes hugging the wall. In no way did they feel that their system of living was sub-standard.

Some elderly couples show me average figures of total income amounting to $1950.00, and yet they refuse to believe that they are on the verge of indigency. Such people generally rent a mere single room, with kitchen and bath privileges thrown in on a catch-as-catch-can basis.

The results of my inquiries have led me to advocate the following: "Spend no more on rent per month than you earn or receive in a week." A catastrophic illness and long hospitalization would soon deplete the financial resources of any of the couples just described. Then a mortgage for some, and welfare grants for others, would become a necessity.

An income of $3000.00 per year for many conservative old people would tide them over most bumps. I now preach this figure as a minimum retirement allowance to ambitious couples in their forties and fifties who are planning the future for their sixties and seventies by savings, investment, social security and part-time work or insurance plans. Eventually, geriatric hospitalization and medical service plans can be afforded by people in this salary classification.

A geriatric home with motel-like units for married couples, possessing a central dining hall, a crafts room and a recreational area, could be planned for 50 families at the low cost of $300,000.00. A couple could be housed and fed for $300.00 per month, including hospitalization and medical service group insurance. This would provide grand "minimal living," with many compensations and a community of interests thrown in.

THE SHELTERED WORKSHOP

Donahue, Rae, Hunter and others have done yoeman service in the Jackson County Medical Facility and in the Washtenaw County Hospital. Before establishing Sheltered Workshops in these two counties, preliminary work had to be carried out with respect to complete physical examinations, evaluations by the Department of Physical Medicine at University Hospital, Ann Arbor, determinations of endurance, gauging of residual skills, and missionary endeavors in arousing the desire for action and accomplishment on the part of the old people involved.

"Nuisance" jobs from local manufacturers were scheduled according to a Henry Ford production system. Feeble hands of former stroke victims became active again. Each man or woman in a "two to three-hour day" can now perform a portion of the job as it comes along. Some bore holes, others sand, or one may glue a label; thus a partial assemblage is accomplished. Final gauging, inspection and rejection occurs before boxing and shipping. There is dollar compensation on a small scale. Workshop quarters, food, overhead, management, accounting and raw materials are all gifts; but a payroll does exist. With the eagerness of

children, the coins in the envelope are counted over and over again. One feeble old man bought a Thrift Shop bathrobe with the first pay he had received in years. Everytime a car came down the country road, he made an effort to strut on the porch or across the lawn, just to let the passersby realize that progress was being experienced in his particular bailiwick.

Similar worthy activities are carried on in the Good Will Industries and Community Center Projects. The Ann Arbor Exchange Club, under Dr. Clarence Crook's direction, has served as local financial father for community plans of interest, and has advanced money to begin a payroll. Dr. Wilma Donahue and her group have planted a rehabilitation seed that will eventually take the nation by storm. A rehabilitated old person may find the "joy of renewal" even in his own home or in a Community Memorial Center.

BIG CORPORATIONS

Bigness is not wickedness but rather opportunity, and opportunity leads to greatness. In recent weeks I have been in correspondence with large corporations in this country, covering such fields as automobiles, chemicals, explosives, synthetics and agricultural implements. Our exchanges dealt with industry's approach to the geriatric problems of workers in the executive, white-collar, skilled, and semi-skilled classes. In no case could I find a company not alerted to, nor sympathetic with its aging employees.

The average industry on my list considers age 65 as a starting point for retirement on a pension, although age 60 may be selected if backed up by thirty years of service. A revaluation of skills and health may extend the age to 68. In some areas the executive class may be subject to recall following retirement, as consultants. Also certain skilled artisans may secure part-time employment, although "retired." Permanent disablement at age 65 may permit retirement on a pension after fifteen years of employment.

I was particularly pleased to observe a "preparation for retirement plan" exercised by a few corporations, though not on a universal basis. This plan creates a positive approach to retirement, months or years before the event, easing emotional and physical adjustment to the changed state. The blank letdown is thus avoided. Financing, hobbies, art, drama, new skills, part-time employment, gardening, recreation, exercise, travel—all are discussed in a preparatory course of lectures or demonstrations.

Many a vigorous craftsman bemoans that the age of 65, by the stroke of the clock, turns him from a trencherman into an oldster. It is to be hoped that our "salable services" may be able to have this extended to at least the age of 70. Our economy, in spite of some recent recessions may soon require such a formula.

You might be interested to know exactly how a pension is figured. Here is a fair example of a non-contributory program:

> 1.1% × average monthly income for 10 years × years of employment = pension. Let us consider $500.00 per month as the last 10 years' average, applied to a worker who has completed 40 years of service. Then, 1.1% × $500.00 × 40 = $220.00 per month pension.

To make a shortened (*e.g.*, 15-year) service yield a pension in spite of time prejudice, this formula is used:

$$\tfrac{2}{3}\% \times \text{average monthly 10-year pay} \times \text{years} + \$45.00.$$

$$\text{Thus } \tfrac{2}{3}\% \times \$500.00 \times 15 + \$45.00 = \$95.00.$$

The method selected must yield the best figure for the retiree. Social security benefits are collected in addition to pension.

Every pensioner who has residual health should make use of his physical strength. Constructive hobbies, zestful exercise and part-time employment will tilt the balance to one side, but the opportunity to give assistance to others less fortunate in life will even up the beam. Formerly, an old man would often send pennies to the missionaries in far-off lands. Nowadays, he is a Johnny-on-the-spot missionary every day that he has the strength to draw on his pants. The same, of course, applies to the women.

ANN ARBOR'S SANTA CLAUSERIE

At 1315 Franklin Boulevard in Ann Arbor, Michigan, there resides a little man named Albert Warnhoff, now in his seventies, who is shortly completing fifty-seven years in his recreational specialty of creating toys for children. This began in his days of hobbledehoy and has continued into the era of wisdom and reflection.

I have inspected his "garage warehouse" and "basement shop." Eight power tools and much hand ingenuity cut out the parts for assemblage and finishing. The works of an eight-day clock will drive a Monk's pumping operation at the well. Miniature windmills, small sturdy stools, doll cradles and beds—all are in production now for the eventual Christmas trips to some 20 hospitals and institutions, not forgetting the School for the Blind in Lansing. The blind students "feel out" their toys and the face of their benefactor. Photographs by Life Magazine demonstrate their delicate, appreciative and investigating fingers. About 2000 toys are in the budget for this year. Viewing the miniature architect among his mountain of raw materials and finished products, one is reminded of a wise Mickey Mouse about to fabricate a palace from a world of corn cobs.

This man was once in the lumber and carpentry business, and is now a part-time neighborhood school policeman, and recipient of honors from his Governor and his President. He accomplishes a full day's work. Says he, "To wear out is better than to rust out."

SUMMARY

The purpose of this paper is to surcharge the field of geriatrics with the adjective "unlimited." Memoirs concerning some successful personalities in their later years are presented. Mention is made of the accomplishments of the Du Pont retirees whose talents are available for younger strugglers.

Part-time work and new skills may enter life after retirement, both in the artisan and professional fields.

The financial angles of "minimal living" are presented, and plans for a geriatric motel home are outlined. The sheltered workshops of Donahue, Rae and Hunter in the field of rehabilitation are discussed.

A summary of pension and retirement plans of certain large corporations is presented. Pre-retirement counselling is urged.

Tribute is paid to the Warnhoff Santa Clauserie in Ann Arbor.

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Abstracts of Current Literature

CARE AND TREATMENT OF THE SENILE AND ARTERIOSCLEROTIC MENTAL PATIENT
Beckenstein, N. *Dis. Nerv. System.* **20:** 102 (May) 1959.

Psychoses of the senium accounted for greater percentages of first admissions to New York State mental hospitals and to the Brooklyn State Hospital in the year 1957 than they did in 1943. When the results of studies made in 1943 and in 1957 on 100 consecutive patients with senile psychoses and 100 with psychosis with cerebral arteriosclerosis in each year were compared, the following facts were found: Patients admitted in 1957 were older. The reasons for admission were similar; the most frequent was inability to care for the patient longer at home or in an institution such as a general hospital, nursing home, or home for the aged. Patients were admitted to the Brooklyn State Hospital after a longer stay at home in 1957 than in 1943. This probably occurred because of better understanding of elderly persons and a greater degree of tolerance toward them, better health services, the widespread use of tranquilizers and antibiotics, social security benefits, and the establishment of "golden age" clubs and day-care centers for elderly persons. The number of patients leaving the hospital in both studies was the same. Fewer patients in the 1957 series died, so that more remained in the hospital. The percentages of patients who died were approximately the same at one month, but the percentage of patients who died in the six-month period after admission was greater in the 1957 series. The patients who have remained in the hospital are to be the subjects for a study to determine how many can be returned to their homes or sent to another type of institution if guidance in their care is provided. The objective is to devise means whereby aged persons with mental disorders can be cared for at home without being admitted to a state mental institution, and a way to keep at home those who have improved and have been discharged from such an institution.

KRITISCHE BETRACHTUNGEN ZUR HOCHDOSIERTEN PREDNISOLON THERAPIE BEI MALIGNEN HÄMOBLASTOSEN (OBSERVATIONS ON HIGH DOSAGE PREDNISOLONE THERAPY IN MALIGNANT HEMOBLASTOSIS).
Böhnel, J., and Stacher, A. *Klin. Med.* **14:** 19, 1959; through Ciba Literature Review **4:** 199, 1959.

The use is reported of large doses of prednisolone in myeloblastic leukemia, lymphogranuloma, lymphosarcoma, and thymus carcinoma (11 cases in all). Prednisolone was given in a daily dosage of 250 mg. for one to two weeks, sometimes concomitantly with cytostatic agents. The dosage was then reduced to 15 to 45 mg. and ACTH was administered for a short time. After a gastric ulcer, which previously had caused no symptoms, became manifest in 1 patient, all patients were given antacids in addition. An enhanced hemorrhagic tendency due to thrombopenia occurred in 7 patients. The improvement brought about by prednisolone in all the forms of lymphogranulomatosis was far greater than that achieved by methods hitherto employed. This treatment with large doses of prednisolone should be used only in patients who have failed to respond to cytostatic agents and to small doses of cortisone. Even then, large doses of prednisolone should only be given in cases of lymphogranulomatosis and lymphosarcoma, since in acute leukosis the advantages of the high dosage levels do not nearly offset the increased risk of complications.

HEART-DISEASE AND INFLUENZA.

Bourne, G., and Wedgwood, J. *Lancet* **1:** 1226 (June 13) 1959.

Influenza appears to have a definite although transitory toxic effect upon the myocardium. This may be (as suggested by Saphir, 1941) because it brings about cloudy swelling or some lesser change. In 14 cases reported, influenza appeared to have caused cardiac disability. The average age of 57 years among these patients suggested that prior to influenza their hearts might not have been normal. Auricular fibrillation was precipitated in 8 patients. In 4 of them, the electrocardiogram gave some indication of an underlying myocardial defect. Auricular flutter occurred in 1 patient. Symptoms of coronary artery disease appeared in 2 patients. Two patients with angina of effort due to coronary artery disease became worse after an attack of influenza. In 1 patient, influenza apparently caused an inversion of the T-wave in the left ventricular leads (electrocardiogram). In the last patient, a long history of premature beats, and later of paroxysmal tachycardia, indicated the presence of a slight chronic cardiac abnormality.

SENESCENCE IN OPHTHALMOLOGY.

Bürger, M. *18th Internat. Congr. Ophthalmol.*, Brussels, 1958; through Excerpta Med. (Gerontol. & Geriatrics) **2:** 33, 1959.

Many years of study have taught the author that aging begins as early as at conception, and ends with death, which justifies the ancient saying: "Nascentes morimur." The main difficulty in measuring the aging processes is that the changes of the body and its tissues, including the eye, which last all through life, interfere with the daily happenings of metabolism. Our efforts should therefore be aimed at finding tissues which are largely exempt from these daily metabolic processes. The metabolism of man and animals is connected with oxygen consumption. The less oxygen is supplied to the tissue, the less intensive is its metabolism. According to this principle, tissues can be divided into those with a low oxygen metabolism—or bradytrophic tissues—and those with a high oxygen metabolism—or tachytrophic tissues. Among the bradytrophic tissues are the cornea, the lens, cartilage, bone, teeth, certain parietal layers of the large vessels, the intervertebral discs, and the tympanic membrane. The bradytrophic tissues have a common fate: with increasing age their water content decreases. This desiccation process leads to densification, which is chemically characterized by an increase of the protein content. The densification makes the exchange of nutrients and the transport of waste products more difficult. Consequently, as age advances, deposits of so-called "slag substances" develop, for which the author has chosen calcium as an inorganic and cholesterol as an organic model. If measured with the Warburg method, all bradytrophic tissues show a low oxygen consumption and for this reason are particularly suitable for grafting, as demonstrated by the transplantation of cadaveric cornea into living persons and by the grafting of vessels of dead into living patients. The increase of nitrogen-containing substance has been demonstrated in the bovine cornea and lens. The increase of slag deposits, especially of cholesterol, is demonstrable in animals aged one day to 17 years. The result of the deposition of slag substances, especially of lipids, is characterized by the production of gerontoxon, which is rarely absent at microscopic examination of the tissues of aged persons. The bradytrophic tissues are not only chemically equal as to their fate at advanced age, but also functionally. This is clear from a comparison of the quotient of the pulse wave velocity of the radial artery and the aorta with the course of the accommodation range in diopters during life. As age advances, the quotient of the pulse wave velocity is decreased almost parallel to the accommodation range. This seems to prove that the processes in the lens and the bradytrophic layers of the vascular walls are identical and lead to the same functional behavior. In the bovine vitreous also, chemical and spectrophotometric methods of examination show changes due to aging.

SEVERE HEMORRHAGE AS A COMPLICATION OF DIVERTICULITIS.
Carney, H. M. *South. M.J.* **52:** 499 (May) 1959.

Massive hemorrhage from the colon in elderly persons in the absence of demonstrable disease elsewhere in the bowel is almost always due to diverticular disease. Such hemorrhage is seldom due to carcinoma. The reports of 6 cases of diverticulosis complicated by massive hemorrhage are presented. The plan of management formulated is as follows: 1) Determination of the hemoglobin level, hematocrit, bleeding time, clotting time, clot retraction time, and prothrombin time. 2) Sigmoidoscopic examination whenever feasible, although it has been of little assistance except to detect the presence of a bleeding polyp. 3) Roentgenographic examination with barium given orally for studies of the stomach and duodenum. A barium enema is given sometimes without adequate preparation. 4) Blood transfusion is used as indicated. When more than 200 cc. of whole blood is necessary, or active bleeding continues longer than twelve hours, resection of the affected area is performed.

THE HEART LUNG COEFFICIENT IN OLDER PEOPLE.
Cowan, N. R. *Brit. Heart J.* **21:** 238 (Apr.) 1959.

The value of the heart lung coefficient in clinical medicine has been assessed with reference to 242 men and 190 women, aged 60 to 89 years, who were in good health. The tenth and ninetieth percentile limits of the heart lung coefficient for the age groups 60–69, 70–79, and 80–89 are for men 0.40 and 0.48, 0.42 and 0.50, and 0.42 and 0.52, respectively. The corresponding values for women are 0.45 and 0.53, 0.46 and 0.56, and 0.48 and 0.58. The application of the ratio of 1:2 to older women as a level of normality will give misleading information concerning the existence of cardiac enlargement. Both sexes show a significant positive correlation between the heart lung coefficient and age. In men this is due to an increase in the maximum transverse diameter of the heart with age, and in women it is the result of a significant negative correlation between the maximum transverse diameter of the chest and age. Further investigation is necessary to explain the increase in the heart lung coefficient with age in women. (From author's summary.)

I DISTURBI SENILI DEL RITMO CARDIACO E GLI ESTRATTI DI CUORE EMBRIONALE (EMBRYONIC MYOCARDIAL EXTRACTS IN SENILE CARDIAC ARRHYTHMIAS).
Destrem, H. *Gior. Gerontol.* **7:** 200 (March) 1959.

Five cases of arrhythmia in patients aged 76 to 86 years were cured by means of injections of embryo heart. In 2 cases the arrhythmia was caused by auricular hardening in a purely senile heart. Attention is called to the fact that many cases of senile arrhythmia are connected with cellular exhaustion affecting cardiac tissue, an exhaustion implying disordered metabolism as yet to be defined but independent of the vascular deterioration of the muscular tissue that is more or less evident in old age. Extracts of embryo heart appear to contain some metabolic compensating factors that are useful particularly in stimulating senile hearts in which the different cellular elements undergo (as is the case of all tissues in old age) a potential deficiency that cannot always be compensated for satisfactorily by cardiac stimulants and rhythm-regulating agents. At present, injections of embryo heart, compared with the usual therapeutic measures, appear to be a valuable physiologic aid in strengthening the heart in advanced senility. (Authors' summary.)

AN ALARMING SIDE EFFECT OF TOFRANIL.
English, H. L. *Lancet* **1:** 1231 (June 13) 1959.

A coarse tremor of all four extremities that commenced suddenly, that was little affected by attempts at voluntary movement, and that was present at rest occurred in 3 women aged 76, 72 and 73 years, respectively, when the dosage of Tofranil (known in the United

States as Imipramine) given for depression reached 250 mg. daily. These were among the first 6 cases treated with the drug. No other relevant neurologic signs were found. The patients were unable to stand and fell down, one of them sustaining a fracture. After discontinuation of the drug, the tremor subsided. Tofranil could then be given in smaller dosages without producing tremor. The depression in 1 patient was not alleviated by the drug, but it was slightly alleviated in 1 and improved in the other. Reduction in dosage in a fourth patient probably prevented the development of tremor. This experience suggests that treatment with Tofranil should be undertaken with caution in elderly patients, and especially if the presence of organic changes is suspected.

PRIMARY LYMPHOSARCOMA OF THE STOMACH. A CLINICAL STUDY OF SEVENTY-FIVE CASES.

Friedman, A. I. *Am. J. Med.* **26:** 783 (May) 1959.

An analysis is made of 75 patients with primary lymphosarcoma of the stomach, followed for periods ranging from one month to twenty years. Sixty-four had histologically verified small round-cell lymphosarcoma. Eleven had reticulum-cell lymphosarcoma. No characteristic clinical or laboratory findings could be discerned. The finding of normal or high values for free hydrochloric acid in the presence of large, evidently malignant lesions of the stomach may suggest lymphosarcoma. Perforation occurred in 11 cases (14 per cent). Cases with this complication offer the poorest prognosis. The pathologic appearance of lymphosarcoma is multiform-infiltrative, ulcerative, nodular, polypoid, and combined lesions. The ulcerative form, occurring as a shallow, localized ulceration, was present in 42 per cent of the cases, the most frequent type encountered. Involvement of the duodenum was noted in 6 patients, of the esophagus in 3. Fifteen patients (20 per cent) are alive more than five years after the diagnosis was established, or died after five years from other causes with no evidence of recurrent lymphosarcoma. Seven patients are alive and presumed to be cured more than ten years after surgery, with no evidence of recurrence. Because recurrences appeared as late as nine years following treatment, the prognosis in gastric lymphosarcoma must be guarded. The most effective program of treatment appears to be definitive surgery followed by radiation. Rarely, a patient may be cured by roentgen therapy alone, more frequently by adequate surgery alone. The prognosis in cases of gastric lymphosarcoma and lymph node involvement appears to be more favorable than in cases of carcinoma of the stomach with comparable spread. (From author's summary.)

CHOLINE ESTERASE ACTIVITY IN RHEUMATOID ARTHRITIS.

Hammarsten, G.; Jonsson, E.; Lindgren, G., and Nettelbladt, E. *Acta rheum. scandinav.* **5:** 42, 1959, Fasc. 1.

Albumin metabolism in rheumatoid arthritis was studied by determining the choline esterase activity in the plasma of 200 patients in different stages of the disease and with disease of varying activity. This determination is believed to be a better measure of albumin synthesis than is the albumin content of the blood. The choline esterase activity was lower the more advanced the disease. It was also lower in rheumatoid arthritis of long duration than in that of recent onset. The slope of regression lines referring to the choline esterase activity and to hemoglobin values, the sedimentation rate, and the serum iron content agreed with results to be expected from the first two findings. These findings indicate that in advanced rheumatoid arthritis the albumin synthesis in the liver is lower than in earlier cases. The question of whether this alteration in protein metabolism is due to a disturbance specific to rheumatoid arthritis is not answered.

CLINICAL AND PHARMACOLOGICAL OBSERVATIONS OF THE EFFECTS OF 9-alpha-BROMO-11-beta-KETOPROGESTERONE IN PATIENTS WITH CARCINOMA OF THE BREAST.

Jonsson, W.; Colsky, J.; Lessner, H. E.; Roath, O. S.; Alper, R. G., and Jones, R., Jr. *Cancer* **12:** 509 (May–June) 1959.

Thirty-four patients with advanced mammary carcinoma were treated with 9-alpha-bromo-11-beta-ketoprogesterone (BOP) known as Braxorone. Objective and subjective evidence of improvement occurred in 7 patients all of whom were under 55 years of age. An objective response consisted of: progressive reduction in size of superficial tumor masses, reduction in size of pulmonary lesions, recalcification of osteolytic bone lesions, reduction in fever due to the tumor, and correction of hypercalcemia and hypercalciuria. In addition, 9 patients showed subjective improvement. Three of these were over age 55. No patients in this group improved objectively. The duration of objective improvement was 1.5 to 5.5 months. Subjective improvement was usually apparent in one to three weeks after the start of therapy. Three patients who had previously had an excellent response to testosterone had the most sustained benefit from BOP. Two patients who failed to respond to testosterone and castration were among those improved with BOP. One patient who had responded well to bilateral adrenalectomy and had a prolonged remission with testosterone experienced only subjective improvement under treatment with BOP. A second patient who failed to improve in response to oophorectomy, testosterone and adrenalectomy, showed no improvement during treatment with BOP. The physiologic effects of BOP included a tendency to fluid retention, a fall in serum calcium concentration sometimes accompanied in patients with skeletal metastases by a rise in the serum alkaline phosphatase level, hypercalcemia in 3 patients but a reduction in the serum calcium level in 1 patient who initially had marked hypercalcemia, and a fall in the eosinophil count in patients with a fasting count of more than 100 per cu. mm. before treatment. No significant change occurred in the fasting blood sugar level, the insulin requirement of diabetic patients, or urinary 17-ketosteroid excretion. Hirsutism, present as a result of the administration of androgen, regressed. No consistent change was observed in the cytology of the vaginal epithelium in patients in whom Papanicolaou smears showed evidence of estrogenic activity. No untoward effects were noted. These results indicate that further experimentation with this and other agents possessing progestational activity is warranted in mammary carcinoma.

VALUE OF THE VOICE IN DIAGNOSIS OF MYXOEDEMA IN THE ELDERLY.

Lloyd, W. H. *Brit. M.J.* **1:** 1208 (May 9) 1959.

Myxedema is likely to be overlooked as a cause of symptoms in persons over 60 years of age. Attention is drawn to changes in the voice as an important clinical sign. These are divided into two main groups: 1) changes in quality consisting of low pitch, an increased catarrhal or nasal quality, a clotted quality, huskiness, and harshness; and 2) changes in diction including difficulty in articulation, slow and deliberate speech with stumbling and slurring of certain words, sometimes rapid speech with inability to retain normal spacing of words so that slurring of groups of words occurs (most patients who slur groups of words usually show a mixture of rapid and slow diction), loss of the ability to sing, and an alteration in pitch. The slurring is highly characteristic. In the 5 cases of myxedema described, the patients had the symptoms commonly associated with myxedema: increasing weight, constipation, falling hair, sensitivity to cold, dry skin, difficulty in walking, vague limb pains, failing of memory and concentration, slow thought, and dizzy spells. However, the correct diagnosis, when they were first seen, was suggested by the voice. Serial voice recordings, serial determinations of the basal metabolic rate, and photographs are recommended as diagnostic aids in doubtful cases of myxedema, and partiuclarly in elderly patients.

IRON TREATMENT OF ANEMIA IN RHEUMATOID ARTHRITIS.
Lövgren, O. *Acta rheum. scandinav.* **5:** 66, 1959, Fasc. 1.

The oral administration of iron for the treatment of hypochromic anemia occurring in rheumatoid arthritis is valueless but intravenous iron therapy with a suitable preparation that is free of side-effects is indicated for 3 reasons: 1) low iron values can be raised to normal in many patients by the administration of such therapy for varying periods of time; 2) the effect of corticosteroids is enhanced if the serum iron level is brought to normal prior to their administration. When the serum iron content is normal or has been brought to normal, Lövgren uses an initial daily dosage of 7.5 mg. of prednisone or prednisolone followed by a maintenance dosage of 5 mg. or less per day. Frequently when the effectiveness of corticosteroid therapy has declined, the serum iron value also has declined. In this situation the administration of iron intravenously has allowed corticosteroids again to become effective. 3) Phosphate fractionation in blood and synovial fluid of patients with rheumatoid arthritis has shown that there is an accumulation of a fraction known as "difference phosphorus." Pathologically high values for difference phosphorus appear to be related to pathologically low serum iron levels in rheumatoid arthritis. The phosphorus fraction soluble in trichloracetic acid (total and difference phosphorus) falls after the intravenous administration of iron. This indicates that the iron becomes bound to the phosphate and cannot be taken up in the serum. Thus, an excess of iron seems to be able to affect some of the basic factors involved in rheumatoid arthritis.

AMBENONIUM IN THE TREATMENT OF URINARY RETENTION AND CONSTIPATION.
Mahoney, E. M.; Friend, D. G., and Harrison, J. H. *New England J. Med.* **260:** 1065 (May 21) 1959.

Urinary and fecal retention, alone or together, are occurring frequently as a result of the use of potent drugs for the treatment of a variety of conditions including hypertension and Parkinson's disease. Some ganglion blocking agents and gastro-intestinal tract antispasmodics, for example, may be the cause of these complications. Weakness of the bladder or bowel may occur and complicate treatment in such conditions as chronic overdistention of the bladder, severe infections, disease of the spinal cord, and carcinoma, or following abdominal surgery. These complications, too, are increasing because more people are living to an age during which they have always been prevalent. The cholinergic drug ambenonium (Mytelase), which exerts 5 to 13 times the anticholinesterase activity of neostigmine methyl sulfate, was tested in the management of patients with dysfunction of the bladder or bowel manifested by urinary retention or severe constipation. The drug was unsuccessful in preventing acute postoperative urinary retention even in large doses. It did prove capable of relieving chronic urinary retention or atony of the bowel due to surgery or to drugs. For this purpose it was administered to 20 patients in doses of 20 to 75 mg. per day. The patients became able to void without catheterization or the use of cathartics. Under treatment with ambenonium, patients were able to continue the use, and even sometimes to increase the dose, of the therapeutic agent they had been receiving prior to the complication of retention. No deleterious effects upon the skin, blood or liver were found. Three patients who were receiving mecamylamine simultaneously had a severe reaction that consisted of inability to swallow and muscle weakness which in 1 patient was severe and in another caused the arms to be so limp that they could not be moved. One of these reactions occurred after a dose of 10 mg., the others with a dosage of 25 to 50 mg. per day. As a result of this reaction, it is recommended that ambenonium be given only with extreme caution to patients receiving mecamylamine.

INTRAVENOUS INJECTION OF HYALURONIDASE IN ACUTE MYOCARDIAL INFARCTION: PRELIMINARY REPORT OF CLINICAL AND EXPERIMENTAL OBSERVATIONS.
Martins de Oliveira, J.; Carballo, R., and Zimmerman, H. A. *Am. Heart J.* **57:** 712 (May) 1959.

Edema is one of the multiple factors involved in the myocardial changes that follow an acute coronary occlusion. It is believed that hyaluronidase given intravenously reduces the

edema in the damaged myocardial area, thus decreasing the injury to the cardiac fibers during the hours immediately after an acute coronary occlusion. It is thought also to facilitate the beneficial action of any existing collateral circulation. Hyaluronidase was administered intravenously to 6 patients chosen by rigorous criteria within eight hours after the onset of pain of an acute myocardial infarction. The dosage schedule was 100,000 units of Wydase in 10 cc. of 5 per cent glucose in water intravenously every six hours for twenty-four hours, then the same dosage every eight hours for two more days, and after that the same dosage every twelve hours for an additional two days. In all patients the S-T segment in the electrocardiogram shifted toward normal within two to twenty-four hours; in 5 patients, these changes occurred before the seventh hour. An unusually rapid improvement in disturbances of conduction occurred in 2 patients. The clinical course of all of the patients was uncomplicated and each could be discharged in good condition within four to six weeks. It has not been determined whether the mechanism of action depends upon spreading of the edematous process or upon increased capillary reabsorption. It may be that both conditions participate or that factors as yet unknown are involved. The use of hyaluronidase is also being investigated in experimentally produced acute coronary insufficiency in dogs. Reports on 7 such experiments are included.

HERPES ZOSTER INVOLVING THE URINARY BLADDER.

Meyer, R.; Brown, H. P., and Harrison, J. H. *New England J. Med.* **260:** 1062 (May 21) 1959.

Two cases of urinary retention secondary to herpes zoster involving the sacral segments in elderly women are reported. In each case the development and healing of the mucosal and neurogenic vesical lesions lagged several days behind those of lesions of the skin. Herpes zoster begins in the posterior- or dorsal-root ganglions. An inflammatory process in the latter area apparently has an irritative effect that causes hypertonia of the bladder, whereas a more severe reaction, with extension to the meninges, spinal cord, and perhaps the anterior horn cells, leads to vesical hypotonia and urinary retention. When the parasympathetic fibers innervating the bladder are involved completely with the herpetic lesion, vesical hypotonia results even when a severe inflammatory reaction in present in the bladder. In this situation, the administration of a parasympathomimetic drug will increase detrusor tone and result in a return to normal micturition. The treatment of herpes zoster is symptomatic and supportive, with control of secondary infection. Involvement of the bladder, with neurogenic dysfunction or herpetic cystitis or both, may lead to fulminating infection or a detrusor eventually replaced by fibrous tissue. Sulfonamides should be given for the control of infection of the urinary tract. Severe cystitis should be treated with antibiotics. A parasympathomimetic drug is given to increase detrusor tone and secure the return of normal micturition when the loss of integrity of the parasympathetic innervation is contributing to hypotonia of the bladder. Tidal drainage of the bladder may be of benefit. One of the patients reported was able to void satisfactorily after treatment with 5 mg. of ambenonium intramuscularly every six hours for eight days. The second patient illustrates that bowel and bladder dysfunction may run a protracted course until the neural tissue heals. Methenamine mandelate was given for the control of urinary-tract infection. With the healing of lesions, bladder function was resumed and constipation disappeared.

HEART FAILURE IN PATIENTS WITH HIGH BLOOD PRESSURE.

Mickerson, J. N. *Brit. Heart J.* **21:** 218 (April) 1959.

High blood pressure per se infrequently caused heart failure among 341 patients with high blood pressure and heart failure—an additional cause could be found in all except 10 (3 per cent) of the patients. An additional myocardial injury was required to initiate failure. In half of the cases this was furnished by cardiac ischemia. In an additional 14 per cent, ischemia was probably a contributing factor. Other important causes were valvular lesions, renal disease alone or combined with cardiac lesions, malignant hypertension, and respiratory infections. Renal causes including malignant hypertension were responsible for failure

in 79 (23 per cent) patients in the series. Thirty-three patients with renal lesions and 53 patients with nonrenal lesions died. The primary cause of death was myocardial infarction (29 cases), uremia (20 cases) (these patients had a renal lesion or malignant hypertension), respiratory infection (13 cases), persistent heart failure (10 cases), pulmonary embolus (7 cases), cerebral hemorrhage (5 cases), mesenteric embolus (1 case), and carcinoma of the stomach (1) case). Heart failure developed at an average age of 59 years in men and of 61 years in women. The mortality in men was higher (27 per cent compared with 24 per cent) and they died at an earlier age than women (59 and 64 years, respectively). The presence of a renal lesion reduced the average age at death by twelve years and doubled the mortality rate in comparison with patients without a renal lesion. Advancing age did not affect the outcome in patients with renal lesions (76 per cent of these patients were below the age of 60 years). Advancing age was associated with a slight increase in the mortality rate in patients without a renal lesion. A probable but not significant increase in mortality was found with increasing blood pressure among the women, and also when all patients were considered as a group. This worsening of the prognosis was shown to be due to the presence of a renal lesion rather than to the height of the blood pressure. Significantly, no ganglion blocking agent had been administered to patients in whom no precipitating cause of heart failure could be found. The inability of the coronary arterial flow to keep pace with the work demands of a hypertrophied myocardium probably accounted for the onset of failure. Hypotensive therapy might possibly have averted heart failure in these patients.

ON THE METABOLISM OF AMINO ACIDS AND PROTEINS IN RHEUMATOID ARTHRITIS.
Nettelbladt, E. *Acta rheum. scandinav.* **5:** 49, 1959, Fasc. 1.

The free amino acids, arginine, histidine, lysine, glycine and threonine, were present in a concentration lower than normal in the serum of 50 patients with rheumatoid arthritis. An investigation of the amino acid composition of the albumin and euglobulin fractions of the serum proteins in these patients showed it to be normal.

REDUCTION OF SERUM CHOLESTEROL LEVELS AND beta-LIPOPROTEIN CHOLESTEROL LEVELS BY NICOTINIC ACID.
Parsons, W. B., Jr., and Flinn, J. H. *A.M.A. Arch. Int. Med.* **103:** 783 (May) 1959.

Reported is a long-term study of the administration of nicotinic acid, with data on fifty-six weeks of treatment in 44 patients. Group 1 patients started in the first year of the study and had average pretreatment serum cholesterol levels above 270 mg. per 100 ml. Group 2 patients started in the second year of therapy and some of them had normal total cholesterol levels but the beta-lipoprotein cholesterol fractions (BLC) or the beta to alpha-1 lipoprotein cholesterol ratios were elevated. Thirty of the 44 patients of average age 50 years were men, and 14 women. The clinical conditions included previous myocardial infarction, angina pectoris, arteriosclerosis obliterans, previous cerebral infarction, diabetes mellitus, xanthelasmata, xanthoma tendinosum, and premature arcus senilis. No vascular diagnosis or physical evidence of hypercholesteremia was present in 9 patients. The dosage was 3 Gm. of nicotinic acid daily, with an increase of 4.5 Gm. if hypercholesteremia was still present at twelve weeks, and to 6 or 7.5 Gm. if it remained at six to eight weeks after the first increase in dosage. At thirty weeks, nicotinamide was substituted in equal dosage. Following this, a preparation containing in addition to nicotinic acid, ascorbic acid, riboflavin, thiamine mononitrate, cobalamin concentrate, pyridoxine hydrochloride and calcium pentothenate, was used (Vastran Forte). The serum cholesterol levels were effectively reduced in the majority of patients in both groups at twelve and at thirty weeks by nicotinic acid. Nicotinamide proved ineffective. The averages of the beta to alpha-1 ratios and the BLC fractions were reduced to normal by nicotinic acid. The alpha-1 fraction was increased slightly but not as much as the beta fraction was reduced. This was taken to represent a shift in cholesterol from one lipoprotein fraction to the other. The beta to alpha-1 ratio

and the BLC frequently were normal after treatment when the total serum cholesterol level remained above normal. The data suggest that the beta to alpha-1 ratio and the BLC level are more closely correlated with clinical evidence of atherosclerosis than the serum cholesterol level. Considering averages, high cholesterol levels showed greater reduction than initially low levels. The response to nicotinic acid appeared to be highly individualistic and could not be predicted on the basis of age, sex, pretreatment average values, or clinical diagnosis. However, patients with xanthoma tuberosum or xanthoma tendinosum were found usually to be refractory. The only significant side-effects of nicotinic acid therapy consisted of flushing and pruritus which almost every patient experienced during the first week of therapy. These usually subsided after a week, but in 14 patients mild flushing occurred with every dose. Toxicity studies including tests of hepatic function and biopsies of the liver in 17 patients after a year of therapy with nicotinic acid showed no abnormalities. The effect of nicotinic acid upon clinical atherosclerosis remains to be determined.

UNIDIRECTIONAL CURRENT, MODIFIED BY SUCCINYLCHOLINE IN ELECTROCONVULSIVE TREATMENT OF THE AGED.

Rappa, J. E., and Tanowitz, H. *Dis. Nerv. System* **20:** 118 (May) 1959.

Electroshock therapy was administered by a modified technic to 649 selected risk patients aged 50 or over. Many types of symptomatology and many diagnostic categories were represented. When a purely affective component was dominant, fewer treatments were needed and a favorable prognosis was likely. The prognosis was less favorable when delusions, somatic fixations, and gross sensorial defects were present. Contraindications present in 437 patients consisted of some physical disability that constituted a potential source of post-shock complication, particularly of the cardiovascular and skeletal systems. When indicated, specific autonomic drugs and other supportive measures were used in all three phases of treatment. The drugs used in pre-treatment were atropine 0.6 to 2.4 mg., aminophyllin 250 to 500 mg., Digalen, 0.5 to 1.0 U.S.P. unit, Etamon 200 to 300 mg., Benadryl 25 to 50 mg., and quinidine, 200 to 400 mg. The drugs used during treatment were pentothal sodium, or Surital, or Neraval in a dosage of 250 to 400 mg., succinylcholine chloride in a dosage of 20 to 80 mg., and oxygen. Post-treatment consisted of oxygen or aspiration, or both. No one patient received all medications, but all were used at some time. A combination of succinylcholine chloride with oxygen, autonomic drugs, and the use of unidirectional current with the Reiter machine proved effective in preventing complications. Only occasional prolonged apnea and mild transitory dysrhythmia occurred. In contrast, among 7562 patients treated with standard technics, serious complications occurred in a ratio of 1 in 108.

DYSTONIE, ATAXIE, UND STARRE DES VEGETATIVEN SYSTEMS BEI ALTEN MENSCHEN, ZEREBRALSKLEROTIKERN UND PARKINSONKRANKEN (DYSTONIA, ATAXIA, AND RIDIGITY OF THE AUTONOMIC NERVOUS SYSTEM IN AGED PERSONS, PATIENTS WITH CEREBRAL SCLEROSIS, OR WITH PARKINSON'S DISEASE).

Ross, E. *Ztschr. f. Alternsforsch.* **11:** 34, 1957; through Excerpta Med. (Geront. & Geriatrics) **2:** 20, 1959.

Three to four double glucose loads were given at intervals of at least four days to persons over 70 years of age, with normal metabolism and capable of walking (determination by Hagedorn-Jensen's method). In comparison with standard values in younger persons the blood sugar curves were definitely elevated and prolonged. The deviation range in males was much larger than in females, from which the conclusion is drawn that in women over 70 years of age the autonomic nervous system is in balance, but in men over 70 it is not, or not yet compensated. The approximately normal two-peaked type of curve is found in mentally active aged persons, and the one-peaked type is present in patients with dementia due to cerebral sclerosis. This pathologic type of curve was interpreted as a manifestation of

rigidity of the autonomic nervous system. Five-sixths of the patients with Parkinson's disease without reduction of their intellectual capacities showed a normal curve. It is inferred that blood sugar regulation is not dependent upon the corpus striatum. It seems important that in the presence of a physiologically changed hyperglycemia, as seen in old age, latent geriatric diabetes can be diagnosed only on the grounds of an increased fasting blood sugar level and an alimentary glycosuria.

ULTERIOTI RICERCHE SUL METABOLISMO IDRICO NELL'ETÀ SENILE (FURTHER RESEARCH ON WATER METABOLISM IN OLD AGE).

Ruol, A.; Menozzi, L.; Drudi, C., and DeBiasio, B. *Gior. gerontol.* **7:** 68, 1959.

Further research carried out on 23 patients supports the results previously obtained which showed that in elderly patients the total water volume of the body and its single fractions are for the most part normal or increased. An altered balance is also present among the body water compartments, there being a great difference in findings in individual cases. Among factors connected with quantitative and distributive changes in body water in the aged, no importance is given to age or sex. As for body constitution, "brachytype" subjects have a total and fractionated water content higher than that observed in other subjects, not only in absolute value but also in relationship to theoretical weight and body surface. "Longilineal" and "normotype" subjects also have increased water compartments in relation to body surface. This study indicates that in advanced age the fat content of the body becomes strikingly lower than in middle or presenile age because of its remarkable physiologic involution. Consequently, there is a relative and probably an absolute increase in the water content. Other factors, however, may interfere to alter water balance in the aged. Among them is emphasized the alteration through metabolic exchanges of the tissues and the physiologic wearing of the membranes which limit the water compartments. Aldrich, Landis, and Joyle's fluorescein tests, which measure the function of small vessels and tissues, often yielded abnormal findings in this series of subjects, even though not closely connected with the quantitative and distributive changes in water content. (From author's summary.)

MULTIPLE PERIPHERAL EMBOLI IN ATHEROSCLEROSIS OF THE AORTA.

Sayre, G. P., and Campbell, D. C. *A.M.A. Arch. Int. Med.* **103:** 799 (May) 1959.

The case of a 69-year-old man re-emphasizes that multiple vascular occlusions of small arteries may occur from emboli that erode from atheromatous plaques in the aorta. Severe atherosclerosis was present in the aorta. Many plaques had eroded with precipitation of blood which became mixed with cholesterol. Emboli of this material had caused widespread vascular occlusions which were most prevalent in the kidneys and brain. The patient suffered from gout. He had a history of syphilis, and results of serologic tests were weakly positive. It was not determined whether vascular insufficiency in the extremities was due to occlusion of large vessels, or whether such insufficiency and multiple ecchymoses on the thighs and abdomen were due to the occlusion of multiple small vessels. The primary sites for significant lesions caused by eroded plaques appears from various studies to be the kidneys, brain, heart, and extremities. The presence of gout or of a positive serologic reaction for syphilis seems to be fortuitous for this development.

DIE VERÄNDERUNG DER BLUTKÖRPERCHENSENKUNGSGESCHWINDIGKEIT DURCH ANTISTIN AND IHRE DIAGNOSTISCHE VERWERTUNG (ALTERATION OF THE ERYTHROCYTE SEDIMENTATION RATE BY ANTISTINE AND ITS DIAGNOSTIC SIGNIFICANCE).

Schultheiss, E.; Máté, K., and Schultheiss, F. *Wien. med. Wchnschr.* **108:** 911, 1958; through Ciba Literature Review **4:** 137, 1959.

It has previously been observed that the erythrocyte sedimentation rate (E.S.R.) is reduced by antihistamines in the presence of inflammation, whereas this inhibition fails to

take place in a certain proportion of tumor cases. This observation was subjected to detailed study in order to find out whether it could lead to useful conclusions regarding the differential diagnosis of tumors and inflammation. The E.S.R. was determined by Westergren's method, but 0.3 cc. of Antistine was added to the blood beforehand. A blood sample measured in the usual way by Westergren's method and another containing 0.3 cc. of normal saline were used as controls. In the presence of inflammation, a high E.S.R. was reduced by an average of 51.5 per cent following the addition of Antistine. In patients with tumors, however, Antistine caused a marked inhibition of the E.S.R. in only 5 of 19 cases. The complete absence of this inhibitory effect in bronchial carcinoma was particularly striking. Serum protein changes were more pronounced in pulmonary tumors than in other tumors of the same size. Although the simple method of measuring the erythrocyte sedimentation rate after adding Antistine to the blood is not necessarily tumor specific, it can provide corroborative evidence in cases in which a tumor is suspected. It also may indicate to a certain extent whether the tumor is in the lung or in some other organ.

A CLINICAL EVALUATION OF QUINIDINE POLYGALACTURONATE.
Schwartz, G. *Angiology* **10:** 115 (Apr.) 1959.

A new quinidine derivative, the galacturonate, was administered to 38 patients aged 34 to 82 years who presented the classic cardiac indications for quinidine therapy. The arrhythmias present included auricular tachycardia, premature ventricular contractions, auricular fibrillation, auricular flutter, auricular premature contractions, ventricular tachycardia, and sinus tachycardia. Quinidine galacturonate was administered in the dosage regimens used for quinidine sulfate preparations, using a high dosage initially and gradually reducing it at one-day or two-day intervals. A maintenance dosage was used in 14 patients. The initial dosage varied from 200 to 800 mg., given as frequently as every two hours and as infrequently as twice a day. In 27 patients there was conversion to normal sinus rhythm. In 3 patients with auricular flutter or fibrillation, or both, there was no conversion to normal rhythm, but the ventricular rate was reduced. Therapy was discontinued in 1 patient because a pre-existing left bundle-branch block continued to develop after quinidine therapy had caused premature ventricular beats to disappear. In the remaining patients, lessening of the arrhythmia occurred. In several patients with premature beats, the condition could not be completely eliminated but the number of premature beats was reduced sufficiently to be rated a good clinical response. Quinidine polygalacturonate caused no side-actions despite the dosages used. This new compound (Cardioquin) is recommended whenever quinidine is indicated for the control of arrhythmia.

LONG TERM THERAPY OF CORONARY ARTERIOSCLEROSIS.
Shapiro, S. *Angiology* **10:** 126 (Apr.) 1959.

Because no one kind of therapy can correct the multiple factors present in coronary arteriosclerosis, 3 kinds of treatment were used in 65 cases. Forty patients had had a myocardial infarct. The remainder showed abnormal electrocardiographic tracings. Each had repeated attacks of angina pectoris, usually associated with effort. All patients received a vasodilator (pentaerythritol tetranitrate, PETN) and a tranquilizing agent (meprobamate) during the entire observation period, which was of at least eight weeks' duration. Some of the patients were under observation for periods of four months to three years. Thirty-four patients received these drugs alone, with glyceryl trinitrate occasionally for the relief of acute attacks of angina. With a dosage of 10 mg. of PETN and 200 mg. of meprobamate three times daily, anginal attacks lessened in frequency and severity in 11 (32 per cent) of the patients in this group. At the end of eight weeks they were able to resume normal activity. Nineteen patients who had recently recovered from an acute myocardial infarction received in addition to PETN and meprobamate, 5 to 10 mg. of coumadin sodium three times daily. Lessening of the frequency of anginal attacks and decreased need for nitroglycerin took place in 14 patients. The anticoagulant therapy was a continuation of that used during the acute myocardial infarct; it was continued for three to eighteen

months after recovery from the acute attack. Twelve other patients with serum total cholesterol levels above normal received 2 Lenic capsules containing 800 mg. of concentrates of essential unsaturated fatty acids three times daily in addition to PETN and meprobamate. The serum cholesterol levels were reduced after six to eight weeks' of therapy in 4 patients. In 2 of them the reduction occurred after desiccated thyroid had been added to the regimen. Anginal seizures lessened in frequency and severity in 5 of these patients (3 of those who improved also showed a reduction in serum cholesterol concentration). The results warrant further investigation of these modes of therapy and suggest that this may constitute an approach to more satisfactory treatment for coronary artery disorders related to arteriosclerosis.

LA PROFILASSI DELL'INVECCHIAMENTO ALLA LUCE DELLE RECENTI ACQUISIZIONI DELLA BIOFISICA (INFLUENCE OF RECENT BIOPHYSICAL KNOWLEDGE ON THE PREVENTION OF THE AGING PROCESS).

Spolverini, L. *Gior. gerontol.* **7:** 253 (Apr.) 1959.

The studies and research of the past twenty years on the application of biophysical principles to the physiology of the intimate life of body cells are reviewed. In this study is shown the prevailing role of an electric charge on the vitality and function of various cellular components with particular reference to biocolloids. The presence of negative ions permits the biocolloids to remain in a condition of ultramicroscopic particles dispersed in a thin state that assures their action. During adult life, and more so in old age, a gradual decrease of this electric charge occurs. Consequently, the thin micelial dispersion diminishes so that the particles begin to group and, at last, to clot causing the natural death of the cells. Clinical studies and research have now shown that it is possible to modify the electrostatic condition of the cells through breathing of air artificially charged with negative ions by means of a special apparatus. In this way, the life of the cells returns to normal. This permits them to continue their regular function, and delays the clotting process and therefore death. (From authors' summary.)

MIXED TUMORS OF THE SKIN OF THE SALIVARY GLAND TYPE.

Stout, A. P., and Gorman, J. G. *Cancer* **12:** 537 (May–June) 1959.

Ninety-five published cases of mixed tumors of the sweat glands, and 39 from the Laboratory of Surgical Pathology of the Columbia University College of Physicians and Surgeons were analyzed in order to collect information about them and to determine if a malignant change ever occurs in such tumors. The criteria for diagnosis demand that the tumor arise in the skin or from sweat glands and that it be composed of epithelial elements mingled with cartilage and myxoid tissue in such a way that the epithelial cells appear to be continuous with the other elements and not separated by a basement membrane. Age at onset, which could be determined in 78 patients, was usually between the third and fifth decades. The majority of the tumors occur on the face and head, the nose, upper lip, cheek and scalp being most frequently involved. The majority of the tumors in the patients reported were small. They ranged in size from one measuring 1 by 2 mm., to one 12 cm. in diameter. The rate of tumor growth was slow and usually progressed at an even pace. A mean time of seven years elapsed between discovery and removal of the tumor (range three months to forty years). Tumor size did not correlate with duration. One tumor was unique in that it lay beneath the deep fascia of the leg. No explanation for occurrence at this site could be offered. No malignant lesion could be found in a *mixed* tumor of sweat-gland origin.

BOOKS RECEIVED

Receipt of the following books for review is hereby acknowledged. We are glad to publish complete listings of all new books received but such listing must be regarded as a sufficient return for the courtesy of the sender. Books of particular interest will be reviewed in full as time and space permit. Additional information in regard to all listed books will be gladly furnished upon request.

BIOSYNTHESIS OF TERPENES AND STEROLS. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.* and *Maeve O'Connor, B.A.* Cloth. $8.75. Pp. 311. 102 Illustrations. J. & A. Churchill Ltd., London, and Little, Brown and Company, Boston, Massachusetts, 1959.

CARCINOGENESIS. MECHANISMS OF ACTION. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.* and *Maeve O'Connor, B.A.* Cloth. $9.50. Pp. 336. 48 Illustrations. J. & A. Churchill Ltd., London, and Little, Brown and Company, Boston, Massachusetts, 1959.

REGULATION OF CELL METABOLISM. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.* and *Cecilia M. O'Connor, B.Sc.* Cloth. $9.50. Pp. 387. 109 Illustrations. J. & A. Churchill Ltd., London, and Little, Brown and Company, Boston, Massachusetts, 1959.

VA PROSPECTUS: RESEARCH IN AGING. *Veterans Administration. 1959.* Cloth. $1.50. Pp. 125. Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1959.

INSULIN TREATMENT IN PSYCHIATRY. Edited by *Max Rinkel, M.D.* and *Harold E. Himwich, M.D.* Cloth. $5.00. Pp. 386. Philosophical Library, Inc., 15 East 40 Street, New York 16, N. Y., 1959.

NURSING HOME MANAGEMENT. By *Ralph C. Williams, B.S., M.D.* Cloth. $8.50. Pp. 230. F. W. Dodge Corporation, 119 West 40 Street, New York 18, N. Y., 1959.

ARTHRITIS—GENERAL PRINCIPLES, PHYSICAL MEDICINE AND REHABILITATION. Edited by *Edward W. Lowman, M.D.* Cloth. $9.50. Pp. 292. J. & A. Churchill, Ltd., London, and Little, Brown and Company, Toronto, Canada and Boston, Massachusetts, 1959.

THE NEW PSYCHIATRY. By *Nathan Masor, M.D.* Cloth. $3.75. Pp. 155. Philosophical Library, Inc., New York, N. Y., 1959.

PSYCHOTHERAPY AND SOCIETY. By *W. G. Eliasberg, M.D., Ph.D., F.A.P.A.* Cloth. $6.00. Pp. 223. Philosophical Library, New York, N. Y., 1959.

WORLD CONGRESS OF GASTROENTEROLOGY AND FIFTY-NINTH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION. *Washington, D. C. May 25–31, 1958.* Volumes I and II. Cloth. $20.00. Pp. 1363. The Williams & Wilkins Company, Baltimore, Md., 1959.

NEWS AND NOTICES

A STUDY OF RETIREMENT POLICIES AND PRACTICES IN THE AMERICAN ECONOMY

UNDER THE SPONSORSHIP OF THE NEW YORK STATE SCHOOL OF INDUSTRIAL AND LABOR RELATIONS

financed by

A GRANT FROM THE FORD FOUNDATION

It is the purpose of this study to assess the role of retirement policies and practices in the adjustment process of older persons and to examine the impact of these policies on the organizations which sponsor them. The study will be concerned with the retirement policies of industrial organizations and of nonprofit organizations such as schools, colleges, and welfare and government agencies. Of special particular interest will be 1) the extent to which the retirement process is automatic for all, or, if selective, how the selection is accomplished; and 2) the nature and effectiveness of pre-retirement planning programs conducted by industry, trade unions, communities, welfare agencies, and churches.

The transition to retired life has economic, psychological, social and physiological consequences which have led industry, labor and other organizations to experiment with new programs. The present study will seek to describe and analyze some of the existing practices.

The study is designed in three parts:

I. An effort to bring together, in a systematic fashion, the basic and relevant information about retirement practices, personnel policies associated with retirement, and about efforts to facilitate the transition to retirement by planning. The survey will be nationwide and will include employing organizations of all types, including public and private, and profit and nonprofit making institutions.

II. An intensive study of a sample of business firms and other organizations. This will analyze retirement policies and practices and preparation for retirement programs in relation to key factors which shape organization policies and influence operating experience thereunder. Here we shall be concerned with the relationship of retirement policies and experience to such factors as geographic location, type and size of community, nature of the industry and workforce, and extent and nature of union-management relations. Of importance in the analysis will be an assessment of the value and role of pre-retirement planning programs for adjustment to retirement, an examination of the impact of retirement policies on the operation of the sponsoring institutions, and the reaction to retirement of those who retire, as well as of personnel directors, managers, union officials, and rank and file community leaders.

III. An investigation of individual and community attitudes toward retirement. This portion of the study will be carried out in a selected number of communities and will seek to ascertain how the general public views retirement—the stereotypes people have about retirement and retired people, and their criteria of successful and unsuccessful retirement.

The study will be conducted under the direction of:

John W. McConnell, Dean, New York State School of Industrial and Labor Relations, Cornell University.

Edwin B. Shultz, formerly Chief, Labor Relations Branch, Tennessee Valley Authority.

Patricia Smith, Associate Professor of Psychology, Cornell University.

Fred Slavick, Visiting Associate Professor, New York State School of Industrial and Labor Relations, Cornell University.